96-180

PROPOXYPHENE—OVERSIGHT

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT

OF THE

COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE

HOUSE OF REPRESENTATIVES

NINETY-SIXTH CONGRESS

SECOND SESSION

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PROPOXYPHENE—OVERSIGHT

WEDNESDAY, MAY 21, 1980

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2318, Rayburn House Office Building, Hon. Henry A. Waxman, chairman, presiding.

Mr. WAXMAN. We will come to order.

Our hearing this morning is another in the subcommittee's continuing review of the broad and often frustrating aspects of the drug abuse phenomenon in this country. Earlier hearings have illustrated that drug abuse is a public health problem which assumes many forms, knows no age, sex, or ethnic boundaries and is as likely to strike in the form of prescription medicines as illicit narcotics.

The subject of our hearing this morning, propoxyphene, is a drug which has been in general medical use for many years. Since its first introduction in 1957, the popularity of this analgesic has caused it to become one of the most frequently prescribed drugs in America. It is prescribed for the relief of mild to moderate pain and is most frequently dispensed under the Eli Lilly & Co. brand name Darvon.

Despite the drug's popularity, serious, probing questions have been raised as to its effectiveness and, most importantly, its toxicity. In recent years, Darvon and other propoxyphene products have become one of the substances most frequently cited by medical examiners in reports to the Drug Enforcement Administration's drug abuse warning network. During 1979, propoxyphene ranked sixth among controlled substances in the number of drug related injuries reported by hospital emergency rooms.

The extent of Darvon abuse—in terms of deaths as well as hospitalized injuries—continues to be a serious problem and is cause for our hearing this morning.

Concern over the safety of Darvon is not a new issue. Efforts have been ongoing for almost 2 years to place restrictions on the drug's distribution through imposition of controls available through the Controlled Substances Act.

Last June, former Department of Health, Education, and Welfare Secretary, Joseph Califano, declined a petition from the Public Citizen Health Research Group (HRG) to place propoxyphene containing products in schedule II of the Controlled Substances Act. HRG had argued that schedule II controls were necessary to reduce the number of deaths and injuries associated with the drug's use.

While turning down the Health Research Group's petition, Secretary Califano issued a stern warning for Americans to be wary of this popular pain killer, to use it with utmost caution and then only if other alternatives were not available. He also set in motion a number of administrative actions aimed at gathering more information upon which to base a future rescheduling action. In addition, a nationwide public education campaign was initiated which included a commitment from the Eli Lilly & Co. to inform practitioners of the health risks associated with Darvon's misuse.

The United States is not alone in its concern over the extent of propoxyphene related injuries. On April 17, 1980, the United Nations placed propoxyphene in schedule II of the international narcotic schedule. As the United States is a party to the 1961 Single Convention on Narcotic Drugs, it is bound by treaty to adhere to these new international requirements.

Our witnesses this morning will present testimony on three major issues:

One, to what extent is propoxyphene associated with drug related deaths and injuries?

Two, has the educational campaign, initiated by Eli Lilly & Co., been effective in making practitioners more aware of the adverse health effects associated with propoxyphene?

Three, whether information is now available which would support placing more restrictive controls on propoxyphene distribution.

These are critically important questions and I look forward to hearing the testimony of our expert witnesses.

Dr. Carter, I would like to recognize you at this time for any statement you wish to make.

Mr. CARTER. Thank you.

Mr. Chairman, I believe it is important that we view these hearings as part of our subcommittee's ongoing effort to insure that the American people, and their physicians, have available to them the widest possible array of pharmaceuticals that have been proven safe and effective. To this end I hope we can focus these hearings on Darvon as an example of the successes or failures of the scheduling process set forth in the Controlled Substances Act, rather than on the narrow issue of the safety of Darvon.

In that regard, Mr. Chairman, I would like to say that although I strongly support controls on drugs likely to be abused, I believe that it is generally appropriate to rely on the judgment of an individual physician unless there is strong evidence that further controls are needed.

Nevertheless, I am looking forward to hearing from our witnesses today in the hope that they can shed further light on the controversy surrounding this drug.

Thank you, Mr. Chairman.

Mr. WAXMAN. Thank you very much, Dr. Carter

Our first witness is Dr. Sidney M. Wolfe. Dr. Wolfe is the director of the Public Citizen Health Research Group and principal author of a petition to the Attorney General requesting that Darvon and other propoxyphene products be placed in schedule II of the Controlled Substances Act

Dr. Wolfe, we welcome you to our hearing today. We have your prepared testimony which will be made part of the record. [See p. 9.] Please proceed as you desire in presenting your testimony.

STATEMENT OF SIDNEY M. WOLFE, M.D., DIRECTOR, PUBLIC CITIZEN HEALTH RESEARCH GROUP

Dr. WOLFE. Chairman Waxman and members of the subcommittee, thank you for the invitation to present information on Darvon at this hearing.

According to a recent computer printout from the National Institute for Drug Abuse (NIDA), representing drug abuse data from approximately one-third of the country, there have been 3,674 deaths and 26,335 emergency room visits involving propoxyphene since September 1972 when the system was begun. According to a NIDA official, multiplying these data by three will give a reasonable estimate of the total deaths and emergency room visits for the whole country. This amounts to 11,022 deaths and 79,005 emergency room visits involving propoxyphene. This represents more deaths than for any other prescription drug and does not even include the large number of deaths from 1957, when the drug was first marketed, until September of 1972 when the abuse data began to be systematically collected.

That this narcotic drug—tantamount to legalized dope—is a serious public health problem is not arguable. In the remainder of this presentation I will (1) review what has happened since our petitions in November 1978 to ban or tightly restrict the use of the drug; (2) review studies on the types and extent of propoxyphene abuse in this country; (3) briefly review the evidence collected by the U.N. and Interpol, the international police organization, which was used in the U.N. decision to put propoxyphene in International Schedule II.

Finally, just several suggestions as to how to further attack this problem and decrease what is still an awful toll of deaths, addiction and other problems.

As can be seen in the first figure, figure 1 [see p. 10], there has been a very close correlation between the amount of propoxyphene proscribed and the amount of abuse. Between 1976 and 1979, for example, propoxyphene prescriptions—this is, total prescriptions for all products, including Darvon, refills, new prescriptions—the total number fell from 37 million to 24.9 million or a 33-percent decrease, while propoxyphene emergency room mentions decreased from 3,947 to 2,817, or down 29 percent. The year with the biggest decrease was 1979 following our petitions to ban or restrict Darvon, other congressional hearings, and statements by HEW, as you just alluded to, Mr. Chairman.

In table I [see p. 11], it can be seen that there is a decrease in the number of deaths, except for the year 1977, which stood out from both previous and succeeding years in terms of the large numbers of deaths in 1977. One can again see a correlation. According to NIDA, in 1979 we only have data that is accurate for the first quarter and there are 105 deaths in the first quarter.

From 1976 to 1978, the last year with complete death data, there was a 16-percent decrease in prescriptions and a 12-percent decrease in deaths. If you look at the same data from 1977 as the

base period instead of 1976, it looks like a bigger decrease because of the peak in deaths in 1977. There has also been a slight decrease in the number of deaths per million prescriptions from 1977 to 1978 but the main point is that even though things are getting somewhat better, we are still talking about 1979, with probably well over 350 deaths in just the third of the country or a thousand deaths for the whole country, still an awesome toll for a drug that really has very little value, if any, beyond aspirin.

Figure 2 on the bottom of page 3 [see p. 11] shows the time sequence of the decrease in prescriptions that occurred during the entire year of 1979. What can be seen is that the quarter with the biggest decrease was immediately following petitions and Senate hearings and there were subsequent further decreases, with the smallest decrease occurring during the last quarter, which happens to coincide with Lilly's so-called educational campaign.

In a letter from FDA's Dr. Crout to Lilly, this campaign was heavily criticized. One of the things that was brought out in the study done by the FDA was that more than three-quarters of the detail visits in October and November involved giving free samples. This whole pattern involves stemming the decrease of prescriptions by what was supposed to be an educational campaign but what I think looks like a promotional campaign, mainly for Darvocet.

Darvocet is Darvon with acetaminophen and that seems to be the main drug through advertising or other promotion that Lilly is pushing now.

Dr. Crout characterized this as a "standard promotional campaign" and I think that is a very accurate assessment of what the Lilly narcotics sales people did.

Data from NIDA's Action/Warning System looks at drug abuse trends in each city or metropolitan area from which NIDA gets emergency room data and compares the most recent quarters with a base time period. When each of the four quarters of 1979 are compared with the average of the previous six quarters—mid-1977 to December 1978—the following results were obtained: In 12 cities there was no statistically significant change in any quarter of 1979 in propoxyphene abuse. Again we are talking about emergency room visits; in 11 cities there was a statistically significant decrease in propoxyphene abuse; in 1 city there was a statistically significant increase in propoxyphene abuse, and that city, curiously, was Indianapolis. Overall, for the whole country, there was a statistically significant decrease in emergency room propoxyphene abuse as shown in the trends in figure 1, page 2 of our testimony. This statistically significant decrease was shown in the second, third, and fourth quarters of 1979, with no statistical national change in codeine abuse or oxycodone abuse. This last finding is of interest in view of Lilly's quarterly report to FDA describing increased "demand" for oral codeine products in conjunction with decreased utilization of propoxyphene. If one looks at this data that I just mentioned above, it looks as though, independent of whether or not a city goes down or stays the same with propoxyphene the increase in codeine abuse in a few cities is not at all associated locally or nationally with what has happened with propoxyphene.

One of the more disturbing findings in terms of why there is the amount of abuse, including deaths, emergency room visits and

addiction for this drug, comes from a FDA study based on detailed prescription data at the pharmacy level for 2 million people in the United States and projected nationally by FDA. It showed that, first, during 1978 there were 11.6 million propoxyphene users; second, that 72,000 people in the country were getting, as a result of refills, over 360 pills a month or over 12 pills a day, more than twice the maximum recommended dose of 6 per day. This is an amount which has been shown to be sufficient to cause addiction when used regularly. Third, almost half a million people, or 426,000, got over 180 pills a month or more than the maximum recommended dose of 6 per day.

The authors of this paper, commenting on the 72,000 people getting enough propoxyphene to take over 12 pills a day stated that: "If the propoxyphene was consumed according to the prescription refill records, their daily dosage could have averaged 12 or more dosage units. Considering that dependence may occur if patients take as few as 8 to 12 dosage units per day, the implications are obvious."

Given the easy availability of propoxyphene, with schedule IV allowing up to five refills within 6 months without contacting the physician, it is not surprising that there is such widespread abuse of the drug. The following are examples of studies of nontherapeutic use in various age groups.

First, adolescent propoxyphene abuse. Approximately one-fourth of the emergency room mentions for propoxyphene in 1978 involved persons aged 10 to 19. Of the top ranking drugs in DAWN emergency rooms, propoxyphene ranked seventh among the adolescent subgroup and we include in the testimony other information concerning adolescent abuse. There certainly is a suggestion that teenagers can get this drug from their family medicine cabinets, but again, the fact that someone can go back and get another hundred, another hundred, another hundred or whatever of propoxyphene without ever contacting the physician because it is in this loose controlled schedule IV, I think, supports this kind of abuse.

Drug use patterns were analyzed from a group of 365 adolescents referred by the courts because of alcohol problems in King County, Seattle, Wash. Ten percent of the sample population had used propoxyphene illicitly.

Between September 1976 and March 1977 the National Youth Polydrug Study surveyed 2,750 teenagers 18 or younger. Of this number, 488 subjects or 17.7 percent indicated that they had used Darvon or Darvon-N in their lifetimes, making propoxyphene the most frequently mentioned opiate drug. When ranked in terms of prevalence of "regular use", that is, at least once a week, Darvon/Darvon-N was second only to heroin.

In other age groups, a HEW-funded study of a stratified probability sample by region, race, income, et cetera, of 3,024 19- to 30-year-old men, whose names were obtained from the selective services records, found 14.9 percent had used propoxyphene for nonmedical purposes.

In a DEA-sponsored study, 14 drugs being used in a nonmedical setting for nonmedical purposes in 9 sites in the United States were studied for their contagious transmission. These are studies

done by Dr. Chambers and Dr. Hunt and they really showed outbreaks, so to speak, in both ghetto and suburban neighborhoods of teenage use, of this drug, often to get high, because as mentioned before, it is a narcotic, it is similar to methadone and one can, without much difficulty, use it to get high.

Several methadone clinics have reported significant use of propoxyphene by addicts. In 1978 in New Orleans, of 171 urine samples which showed evidence of drugs, 104 or 61 percent were positive for propoxyphene, making propoxyphene the most frequent drug detected. Methadone treatment programs in New Mexico and California reported that about 25 percent of all urine samples showed propoxyphene.

Going now to just a brief discussion that it is often used in combination with other substances. Despite the fact that it is stated in the labeling, in a mild, understated way to beware of using it with other drugs or alcohol. It does not say don't use it with alcohol, don't use it with other psychoactive substances, it just sort of says be aware of it, warn against it. It does not say don't do it. It certainly is done very frequently. [See p. 15.]

In a recent article on Distalgesic (Darvocet-N) use in the United Kingdom, the authors reported that "Distalgesic accounts for most overdoses" and that "it has become an increasingly popular component of self-poisoning cocktails." They concluded that "the rise in incidence of Distalgesic poisonings has followed remarkably closely the recent rise in the prescription rate for analgesics containing dextropropoxyphene" and suggested "restrictions on the availability of the drug" as a means to curb abuse.

Next, I would just like to briefly review some of the information obtained by the U.N. and World Health Organization before they decided to put propoxyphene in International Schedule II. The first information comes from replies received from various governments around the world, in response to requests for information by U.N. Secretary General Waldheim. I list several examples.

Denmark. "Dextropropoxyphene is often encountered in cases of multidrug abuse or in combination with alcohol or prescription medicine."

Philippines. "Abuse of dextropropoxyphene (combined with dipyrone) was found to be prevalent among former heroin users from low-income groups."

Portugal. "Abuse of propoxyphene is growing and should be placed under international control as soon as possible."

The second study was done by Interpol, the International Criminal Police Organization, which sought information from various countries in terms of police seizures. Among the countries they received information from was Argentina as mentioned at the top of page 9. In Belgium a significant incidence of abuse has been noted. Canada, Denmark—also reported a young female addict died from an overdose—Hong Kong—up sharply from 1977 to 1978—Sweden, the United Kingdom, and the United States.

In Canada I have recently obtained information from the chief medical examiner of Saskatchewan, who has met a number of times with Coalition of Coroners from all the Provinces in Canada. They previously did not have good information on Darvon deaths and have recently sought to collect more information. In Ontario

alone, which represents only one one-third of the population of Canada, there were 106 propoxyphene associated deaths in which either accidental or suicide was the mode in 1977. More recent data from Ontario and all other provinces will be available in several months.

According to Dr. McMillan at a December 2, 1979, meeting of the National Association of Chief Coroners, it was unanimously agreed that Darvon should be placed under tight narcotic controls with no refills and no phone prescriptions. Several weeks ago, in light of the U.N. decision to require all 110 countries, including Canada, to at least impose production quotas on the drug, the Canadian National Association of Chief Coroners wrote to Canadian Minister of Health, Monique Begin, asking her to disallow refills and phone prescriptions for propoxyphene.

This is also consistent with the World Health Organization which said that "dextropropoxyphene is liable to similar abuse and production of similar ill effects as the drugs in schedule II of these Conventions (codeine and codeine analogs)."

Last, what can be done? First, banning the drug. For a drug which has been associated with over 11,000 deaths in the United States since 1972 alone and which is no more effective than aspirin, a much safer drug, the optimal course of action remains a total ban on the drug which we will continue to press for. Although deaths have decreased somewhat since 1976 or 1977, whichever you choose, there will still be well over 350 deaths for the entire DAWN system in 1979 or more than 1,000 for the whole country.

At this rate, decreasing as slowly as it is, it is likely that another 10,000 people will die unless something much more stringent is done than has been done in the past.

Second, stopping the use of Federal funds—medicaid and medicare—to kill and addict poor people and older people.

A disproportionate percent of the propoxyphene emergency room mentions—19 percent—and deaths—13 percent—are black people and a substantial proportion of them are medicaid recipients. Using Federal money for a drug which kills and addicts as much as propoxyphene does is in every sense an abuse of taxpayer dollars.

Third, disallowing refills. In the aforementioned FDA study showing 72,000 people to be getting enough propoxyphene to use more than the addicting amount of 12 pills per day, it was found that in the 10-month period of the study, the average number of prescriptions per propoxyphene user was estimated at 2.2. Other estimates have been 1.6 or 1.7 but suffice to say that a large proportion or approximately 40 percent of the total prescriptions filled in this country are refills. They are an important, if not essential, ingredient in supporting the potential in actual abuse of a drug such as propoxyphene. When barbiturates such as Seconal were placed in U.S. schedule II, disallowing refills, a sharp drop in prescriptions and deaths ensued with decreases much larger than seen with propoxyphene after being placed in schedule IV or even after our petitions and the other congressional hearings.

Until and unless this drug is banned or put in U.S. schedule II, physicians should be urged to write "no refill" on all prescriptions. This will greatly reduce the use and abuse of propoxyphene and will help to protect the physician from malpractice.

Last, stop relying on Lilly's educational campaign. Last year when it was decided for the time being not to do anything in terms of banning or putting the drug in schedule II, the FDA turned to Lilly and believed that Lilly was going to conduct a serious educational campaign. It is a little difficult to imagine how such a campaign would exist given the incentives on the part of the company and indirectly on the part of the salesman to sell more propoxyphene and indeed it didn't.

In a February 5, 1980, FDA memo reviewing Lilly's survey, which Lilly interpreted as showing that "physicians have a very high awareness level of precautions applicable to the prescribing of Darvon products," FDA prescription drug labeling staff psychologist Dr. Louis Morris stated that: "Only 20 physicians of the 300 surveyed or 7 percent spontaneously recalled having been informed about the dangers of using Darvon with alcohol. Other precautions, such as use with other depressants or with emotionally disturbed patients were recalled to an even lesser extent." Dr. Morris concluded that "the Darvon educational campaign has not been shown to have had an important impact on physician decisionmaking."

The other kind of survey that Lilly did of physicians was to ask a physician something like, "Do you think that it is not a good idea to give Darvon with alcohol?" and when prompted thusly most physicians said, no. That is not a very good or accurate way of doing a survey. When it was done on a spontaneous basis, the results were disturbingly low.

In summary, Lilly has sold over $1 billion of Darvon products since 1957 and has contributed to the deaths of over 11,000 people and addiction and abuse of even more, with this form of legalized dope. It is not likely that they will voluntarily "do in" this profitable drug. Federal action to ban or much more tightly restrict Darvon is long overdue.

Thank you. I will be glad to answer your questions.

[Testimony resumes on p. 19.]

[Dr. Wolfe's prepared statement follows:]

TESTIMONY OF

SIDNEY M. WOLFE, M.D.
PUBLIC CITIZEN HEALTH RESEARCH GROUP

BEFORE

HOUSE HEALTH SUBCOMMITTEE HEARINGS ON
PROPOXYPHENE (DARVON)

MAY 21, 1980

Chairman Waxman and members of the Subcommittee, thank you for the invitation to present information on Darvon at this hearing.

According to a recent computer printout from the National Institute for Drug Abuse (NIDA),[1] representing drug abuse data from approximately 1/3 of the country, there have been 3,674 deaths and 26,335 emergency room visits involving propoxyphene since September, 1972 when the system was begun. According to a NIDA official[2] multiplying these data by 3 will give a reasonable estimate of the total deaths and emergency room visits for the whole country: 11,022 deaths and 79,005 emergency room visits involving propoxyphene. This represents more deaths than for any prescription drug and does not even include the large number of deaths from 1957, when the drug was first marketed, until September of 1972 when the abuse data began to be systematically collected.

That this narcotic drug[3]--tantamount to legalized dope--is a serious public health problem is not arguable. In the remainder of this presentation I will (a) review what has happened since our petitions in November 1978 to ban or tightly restrict the use of the drug, (b) review studies on the types and extent of propoxyphene abuse in this country, (c) briefly review the evidence collected by the U.N. and INTERPOL concerning international propoxyphene abuse and death data from Canada which led to the recent imposition of production quotas by the United Nations and (d) suggest further measures to attack this problem.

EMERGENCY ROOM VISITS, DEATHS AND PRESCRIPTIONS

As can be seen in Figure 1, there is a close correlation between the amount of propoxyphene prescribed and the amount abused. Between 1976 and 1979, for example, propoxyphene prescriptions fell from 37 million to 24.9 million, a 33% decrease while emergency room abuse mentions fell from 3,947 per year to 2,817, a 29% decrease. The year with the biggest decrease was 1979 during which there was a 19.7% fall in prescriptions and a 16.2% decrease in abuse.

---

1 Data from DAWN (Drug Abuse Warning System) received through 12/31/79 starting in September 1972.

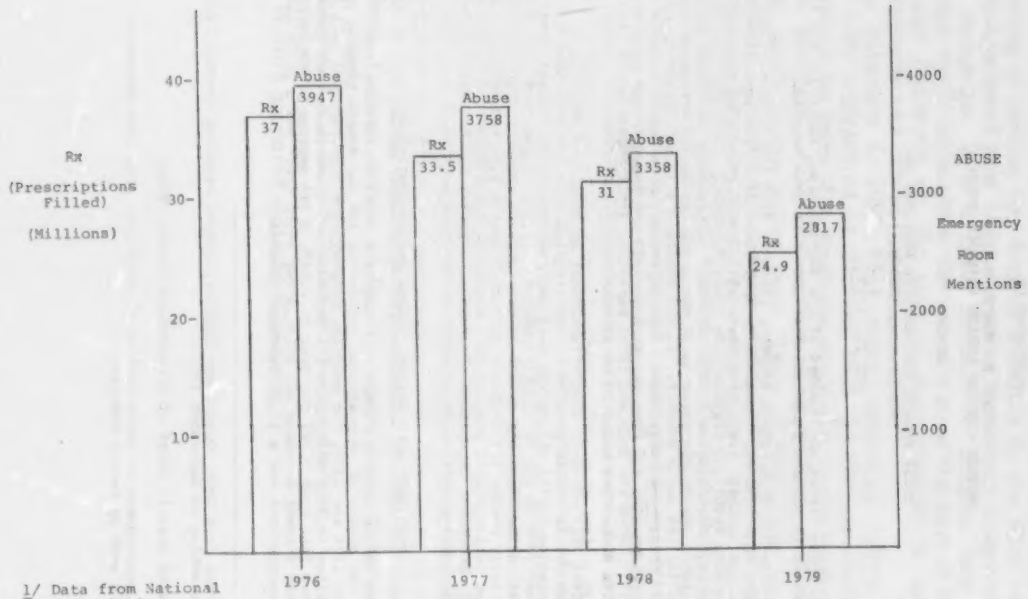
2 Nick Kozell, Chief of Forecasting Branch, NIDA.

3 Propoxyphene is quite similar to methadone and, like methadone, is used by heroin addicts.

READEX FICHE

FIGURE 1

PRESCRIPTIONS FOR PROPOXYPHENE[1/] AND ABUSE OF PROPOXYPHENE[2/] (EMERGENCY ROOM ABUSE MENTIONS)



1/ Data from National Prescription Audit (NPA)

2/ Data from NIDA (HHS)

FROM 1976 THRU 1979: Rx DECREASED FROM 37 MILLION TO 24.9 MILLION (DOWN 33%)
: ABUSE DECREASED FROM 3941 TO 2817 (DOWN 29%)

In Table 1, a generally close relationship can be seen between prescriptions and deaths for the last 4 years except in 1977, the only recent year in which deaths increased despite decreased prescribing.

TABLE I

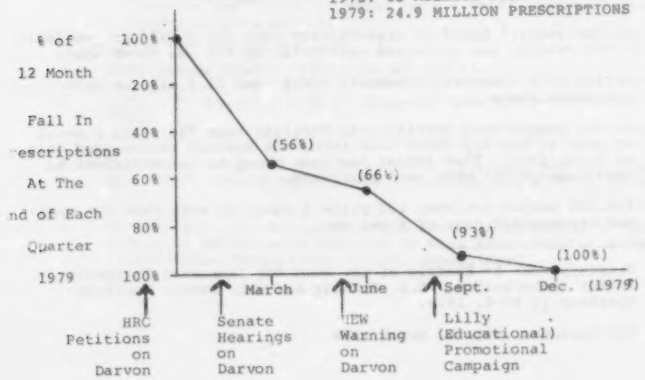
	1976	1977	1978	1979
Millions of Prescriptions	37	33.5	31	24.9
Deaths (1/3 of U.S.)	497	571	440	105(first 1/4 only) Rest of 1979 data not yet complete according to NIDA.

From 1976-1978, the last year with complete death data, there was a 16% decrease in prescription and a 12% decrease in deaths.

Figure 2 shows the time sequence in the decrease in prescriptions for propoxyphene following our November 1978 petitions, Senate Hearings and warnings against using propoxyphene by former HEW Secretary Califano. It can be seen that the so-called "educational" campaign on the dangers of Darvon by Lilly--previously criticized by FDA--(in a March 17, 1980 letter from Dr. Richard Crout to Lilly) was actually successful in one respect. During the last quarter of 1979, when free Darvon samples were given out by Lilly detailmen in 75% of visits (October & November) according to Dr. Crout's letter, there was a lessening of the fall in prescriptions. This fits in with the "standard promotional campaign" character which Dr. Crout used to describe the activities of the Lilly narcotics salespeople.

FIGURE 2

DECREASE IN PROPOXYPHENE PRESCRIPTIONS
FROM LAST QUARTER 1978 UNTIL LAST QUARTER 1979
TOTAL DECREASE = 100% (1.7 MILLION FEWER Rx'S PER QUARTER)
1978: 31 MILLION PRESCRIPTIONS
1979: 24.9 MILLION PRESCRIPTIONS



Data from NIDA's Action/Warning System looks at drug abuse trends in each city (metropolitan area) from which NIDA gets emergency room data and compares the most recent quarters with a base-time period. When each of the 4 quarters of 1979 are compared with the average of the previous 6 quarters (mid 1977-December 1978) the following results were obtained:

--12 cities with no statistically significant decrease in any quarter in propoxyphene abuse (Boston, Buffalo, Kansas City, Miami, Minneapolis, New Orleans, Norfolk, Oklahoma City, Phoenix, San Diego, Seattle and Washington, D.C.)

--Cities with a statistically significant decrease in propoxyphene abuse (Atlanta, Chicago, Cleveland, Dallas, Denver, Los Angeles, New York, Philadelphia, San Antonio, San Francisco)

--City with a statistically significant increase in propoxyphene abuse (Indianapolis)

Overall, for the whole country, there was a statistically significant decrease in emergency room propoxyphene abuse during the 2nd, 3rd and 4th quarters of 1979 with no national change in codeine abuse and a decrease in oxcodone abuse. This last finding is of interest in view of Lilly's quarterly report to FDA describing increased "demand" for oral codeine products in conjunction with decreased utilization of propoxyphene.

In fact, even when an analysis is made in the 11 cities with a decrease in propoxyphene abuse and the 12 cities with no change in abuse, in only 2 of the 11 cities with a decrease in propoxyphene abuse was there a concomitant rise in codeine abuse whereas in the 3 cities without change in propoxyphene abuse, there was an increase in codeine abuse. Thus, decreased prescribing of propoxyphene and the attendant decrease in abuse has not been accompanied either nationally or locally by increased codeine abuse as implied by Lilly.

EXTENT AND TYPES OF U.S. PROPOXYPHENE ABUSE

An FDA study,[1] based on prescription data for 2 million people in the United States, and projected nationally by FDA has shown that:

--During 1978 (February-November) there were 11.6 million propoxyphene users.

--72,000 people were getting (via refills) over 360 pills a month or over 12 per day (more than twice the maximum recommended dose of 6 per day). This amount has been shown to be sufficient to cause addiction[2] when used regularly.

--426,000 people got over 180 pills a month or more than the maximum recommended dose of 6 per day.

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1 Propoxyphene: An Example of the Need for Increased Pharmacist/Patient Interaction. D.L. Kennedy and L.D. Burke: American Pharmacy 10 45-6, 1979.

2 FDA Consumer, page 5, March 1979.

The authors, commenting on the 72,000 people getting enough propoxyphene to take over 12 pills a day, stated that:

"if the propoxyphene was consumed according to the prescription refill records, their daily dosage could have averaged 12 or more dosage units. Considering that dependence may occur if patients take as few as 8-12 dosage units per day, the implications are obvious."

Given the easy availability of propoxyphene, with Schedule IV allowing up to 5 refills within 6 months without contacting the physician, it is not surprising that there is such widespread abuse of the drug. The following are examples of studies of non-therapeutic use in various age groups:

I. ADOLESCENT PROPOXYPHENE ABUSE

--Approximately 1/4 of the emergency room mentions for propoxyphene in 1978 involved persons aged 10-19.[1] Of the top-ranking drugs in DAWN emergency rooms, propoxyphene ranked seventh among the adolescent sub-group.[2] Ranking above propoxyphene were alcohol-in-combination, aspirin, and acetaminophen--not surprising due to the easy availability of these substances. It is surprising, however, to see such a high magnitude of emergencies associated with propoxyphene, considering the unlikelihood of people in this age range having the drug prescribed for them. One possible explanation is that adolescents are obtaining propoxyphene from their family medicine cabinets.

--Drug use patterns were analyzed from a group of 365 adolescents referred by the courts because of alcohol problems in King County, Seattle, Washington.[3] 10% of the sample population had used propoxyphene illicitly.

--Between September, 1976 and March, 1977, the National Youth Polydrug Study surveyed 2,750 teenagers, 18 or younger. 488 subjects (17.7%) indicated that they had used Darvon or Darvon-N in their lifetimes, making propoxyphene the most frequently mentioned opiate drug. When ranked in terms of prevalence of "regular use" (i.e. at least once a week), Darvon/Darvon-N was second only to heroin.[4]

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1 DAWN Annual Report, 1978, pp. 23 and 63.

2 Ibid., p. 23. Only 6.5% of prescriptions are written for people 10-19 (IMS).

3 Schuckit, M.A., and Morrisey, E.R., "Propoxyphene and Phencyclidine (PCP) Use in Adolescents," J. Clin. Psychiatry, 39(1): 7-13, 1978.

4 Farley, E.C. and Santo, Y., "The Abuse of Darvon in a National Sample of Adolescents Admitted to Drug Abuse Treatment Programs," Philadelphia Psychiatric Center, unpublished.

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II. OTHER AGE GROUPS

--A HEW-funded study of a stratified probability sample (by region, race, income, etc.) of 3,024 19-30 year old men, whose names were obtained from selective services records, found 14.9% had used propoxyphene for non-medical purposes. Projected to the total U.S. male population, this suggests that 3 million American men in this age range have used propoxyphene for non-therapeutic reasons.[1]

--In a DEA-sponsored study,[2] 14 drugs being used in a non-medical setting for non-medical purposes in 9 sites in the U.S. were studied for their contagious transmission. Contagious transmission is "the tendency of a psychoactive drug to spread spontaneously among related individuals in peer groups or association groups of some sort without any medical control."[3] Of 926 drug abusers undergoing treatment, 38% had used propoxyphene for its psychic effects. Those who reported using propoxyphene obtained the drug from friends, peers and dealers about 70% of the time and from medical sources approximately 20%. In about 40% of the sites studied, propoxyphene displayed contagious transmission by statistical definition. One of the authors concluded:

> "The importance of contagious transmission is that it is direct evidence of nonmedical use of a drug. If a drug is spreading by interpersonal contact among and within peer groups, its source has escaped from any medical controls (such as prescriptions). . . .The close correspondences between commonness of use, contagious spread, and illicit source of these drugs among treated users are suggestive of nonmedical use typically regarded as abusive."[4]

--Several methadone clinics have reported significant use of propoxyphene by addicts. In 1978 in New Orleans, of 171 urine samples which showed evidence of drugs, 104 (61%) were positive for propoxyphene, making propoxyphene the most frequent drug detected. Methadone treatment programs in New Mexico and California reported that about 25% of all urine samples showed propoxyphene.[5]

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1 O'Donnell, J.A., et al., "Young Men and Drugs: A Nationwide Survey," NIDA, 1976.

2 Hunt, L. and Chambers, C., "Pilot Test of Epidemiological Technique for Detecting Abused Substances in Drug Use Populations," Washington, D.C., RPC Foundation, 1975.

3 Minutes from the Controlled Substances Advisory Committee, April 22-23, 1976, p. 7.

4 Hunt, L., Assessment of Local Drug Abuse, Lexington Books, 1977, pp. 114-115.

5 DEA report to FDA, March 20, 1979, p. 4.

--Tennant reported in detail the non-therapeutic use of propoxyphene hydrochloride which occurred among American soldiers stationed in West Germany during 1969-1971. A survey indicated that "approximately 15-20% of the 180,000 American soldiers in West Germany had used propoxyphene one or more times for non-medical reasons."[1]

--Regarding the reasons for using propoxyphene, only 21% of the emergency room patients in 1978 mentioned their motivation as psychic effect or dependence.[2] Farley and Santo stated that "crisis center clients reporting use of this drug appear to be quite different in this regard: over half of them (51%) indicated they took the drug for its psychic effects."[3]

III. PROPOXYPHENE IN COMBINATION WITH OTHER SUBSTANCES

--The following chart, derived from DAWN data,[4] illustrates the propensity for misuse of propoxyphene in combination with other substances:

PERCENTAGE OF MENTIONS OF PROPOXYPHENE IN COMBINATION WITH ANOTHER DRUG/SUBSTANCE

	1976	1977	1978	1979
Emergency Rooms	64%	63%	64%	66%
Medical Examiners	74%	62%	79%	Data incomplete

--For the years 1976-1979, a total of 322 different combination names were reported in DAWN involving propoxyphene. 168(52%) involved propoxyphene plus an illegal substance.[5]

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1 Tennant, F.S., "Complications of Propoxyphene Abuse," Arch. Intern. Med., 132: 191-194, 1973.

2 DAWN Annual Report, 1978, p. 21.

3 Farley and Santo, op. cit., p. 4.

4 DEA Computer Run, March, 1980 Tape (May 16, 1980).

5 Tims, F.M., Phin, J., Crider, R., "Indicators of Illicit Propoxyphene Use," unpublished, 1979, p. 6.

--In a recent article on Distalgesic (Darvocet-N) use in the United Kingdom, the authors reported that "Distalgesic accounts for most overdoses" and that "it has become an increasingly popular component of self-poisoning cocktails." They concluded that "the rise in incidence of Distalgesic poisonings has followed remarkably closely the recent rise in the prescription rate for analgesics containing dextropropoxyphene" and suggested "restrictions on the availability of the drug" as a means to curb abuse.[1]

U.N. INTERNATIONAL NARCOTIC PRODUCTION QUOTAS ON PROPOXYPHENE: EVIDENCE OF ABUSE IN OTHER COUNTRIES

As of April 17th, the U.S. and 109 other countries became obligated, as signators of the 1961 Single International Convention for Narcotic Drugs to impose production quotas on dextropropoxyphene (the active ingredient). In the last week I have obtained information upon which the World Health Organization recommended this action to the U.N.

1. Replies received by August 31, 1979 from Governments in response to Request for Information by U.N. Secretary-General. (Requests for information on propoxyphene and 4 other drugs.)

DENMARK: "dextropropoxyphene is often encountered in cases of multi-drug abuse or in combination with alcohol or prescription medicine."

NETHERLANDS: "dextropropoxyphene is occasionally found on a drug abuser."

NORWAY: "only dextropropoxyphene has occasionally been found to be a component of pharmaceutical preparations sent for analysis."

PHILIPPINES: "abuse of dextropropoxyphene (combined with dipyrone) was found to be prevalent among former heroin users from low-income groups."

PORTUGAL: "abuse of propoxyphene is growing. . . and should be placed under international control as soon as possible."

SWEDEN: "legally obtained preparations containing dextropropoxyphene have to a limited extent been connected with abuse and suicide."

2. Study by INTERPOL[2] on Appearance of Certain Psychoactive Substances in Illicit Traffic.

In May, 1979, at the request of the World Health Organization, the INTERPOL General Secretariat sent a letter to all INTERPOL countries in order to learn the quantities of drugs--including propoxyphene that had been seized by Police.

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1 Young, R.J. ,Lawson, AA.H., "Distalgesic Poisoning--Cause for Concern," Br. Med. J., 280 (6220): 1045-1047, 1980.

2 "Review of Psychoactive Substances for International Control," July 27, 1979 by INTERPOL (International Criminal Police Organization)

Countries reported by INTERPOL in which seizures by police of propoxyphene had occurred in 1977 and 1978:

Argentina, Belgium "a significant incidence of abuse has been noted", Canada, Denmark (also reported a young female addict died from an overdose), Hong Kong (up sharply from 1977 to 1978), Sweden, United Kingdom and the United States.

3. Darvon Deaths in Canada

The most detailed information on propoxyphene deaths from any country outside of the United States comes from Canada where the Chief Coroners of all Canadian provinces have recently initiated a national survey. According to the Chief Medical Examiner of Saskatchewan, Dr. Stewart McMillan,[1] in Ontario alone--which represents only about 1/3 of the population of Canada--there were 106 propoxyphene-associated deaths in which either accidental or suicide was the mode in 1977. More recent data from Ontario and all other provinces will be available in several months.

According to Dr. McMillan at a December 2, 1979 meeting of the National Association of Chief Coroners,it was unanimously agreed that Darvon should be placed under tight narcotic controls with no refills and no phone prescriptions. Several weeks ago, in light of the U.N. decision to require all 110 countries (including Canada) to at least impose production quotas on the drug, the Canadian National Association of Chief Coroners wrote to Canadian Minister of Health, Monique Begin asking her to disallow refills and phone prescriptions for propoxyphene.

In recommending International Schedule II to the U.N., W.H.O. Director-General Mahler said that "dextropropoxyphene is liable to similar abuse and production of similar ill effects as the drugs in Schedule II of these Conventions (codeine and codeine analogs)."

If anything, certain types of abuse of propoxyphene appears to be at least equal to that seen with codeine. For deaths, dextropropoxyphene is ahead.

--For 1977, propoxyphene was associated with 19 deaths per million prescriptions, codeine with 5.[2]

--A recent review by Dr. Donald Jasinski, Director of the Federal Addiction Research Center showed that the relative abuse incidence for propoxyphene was higher than codeine for DAWN mentions (2.2 times higher) and just slightly higher for other categories he reviewed.[3]

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1 Personal Communication

2 DAWN Quarterly Report, January-March 1978, National Prescription Audit data on prescriptions filled.

3 British J. Clin. Pharmacol., 7, 287-290, 1979.

WHAT CAN BE DONE

1. Banning

For a drug which has been associated with over 11,000 deaths[1] in the U.S. since 1972 alone and which is no more effective than aspirin, a much safer drug, the optimal course of action remains a total ban on the drug which we will continue to press for. Although deaths have decreased somewhat since 1976 (12%), there will still be well over 350 deaths for the entire DAWN system in 1979 or more than 1000 for the whole country.

2. Stopping The Use of Federal Funds (Medicaid and Medicare To Kill And Addict Poor People And Older People

A disproportionate percent of propoxyphene emergency room mentions (19%) and deaths (13%) are in black people[2] and a substantial proportion of them are Medicaid recipients. Using Federal money for a drug which kills and addicts as much as propoxyphene is in every sense an abuse of taxpayer dollars.

3. Disallowing Refills

In the aforementioned FDA study showing 72,000 people to be getting enough propoxyphene to use more than the addicting amount of 12 pills per day, it was found that in the 10-month period of the study, the average number of prescriptions per propoxyphene user was estimated at 2.2.

Refills are extremely important if not essential in supporting the potential and actual abuse of a drug such as propoxyphene. When barbiturates such as Seconal were placed in U.S. Schedule II disallowing refills, a sharp drop in prescriptions and deaths ensued with decreases much larger than seen with propoxyphene after being placed in Schedule IV or even after our petitions and the other Congressional Hearings.

Until and unless this drug is banned or put in U.S. Schedule II, physicians should be urged to write "no refill" on all prescriptions. This will greatly reduce the use and abuse of propoxyphene and will help to protect the physician from malpractice.

4. Stop Relying on Lilly's Educational Campaign

In a February 5, 1980 FDA memo reviewing Lilly's survey which Lilly interpreted as showing that "physicians have a very high awareness level of precautions applicable to the prescribing of Darvon products," FDA Prescription Drug Labelling Staff Psychologist Dr. Louis Morris stated that: "Only 20 physicians of the 300 surveyed (7%) spontaneously recalled having been informed about the dangers of using Darvon with alcohol. Other precautions, such as use with

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1 According to DAWN (Project DAWN Annual Report 1978) 92% of propoxyphene deaths were "drug-induced" (involving an overdose when evidence of a lethal level is found or suspected) and 8% were "drug-related" (drug is a contributing factor.)

2 Project DAWN Annual Report 1978.

other depressants or with emotionally disturbed patients were recalled to an even lesser extent." Dr. Morris concluded that "the Darvon educational campaign has not been shown to have had an important impact on physician decision-making."

In summary, Lilly has sold over 1 billion dollars of Darvon products since 1957, and has contributed to the deaths of over 11,000 people, and addiction and abuse of even more, with this form of legalized dope.

It is not likely that they will voluntarily "do in" this profitable drug. Federal action to ban or much more tightly restrict Darvon is long overdue.

Mr. WAXMAN. Thank you for your testimony.

Dr. Wolfe, is the problem with Darvon deliberate abuse or are problems caused from general use as a doctor would prescribe?

Dr. WOLFE. The problem is abuse but the question is, is there any predictable reason for the abuse. Before the drug was ever marketed it was studied and found to be a narcotic, not as powerful, to be sure, as morphine but recommendations were made that it should be marketed as a narcotic, recommendations which were strongly and successfully fought by Lilly.

But there are a number of attributes, given that it is a narcotic and not a very strong painkiller that lead to abuse. One is it does not work very well and therefore people, even without a drug history, are likely to say, well, I paid my money to the doctor, the drugstore, it didn't work. Even though the doctor recommends one every 4 hours, I will try two. When you get up to twice the recommended dose there are studies showing it is addicting. The fact that a number of people can be and have become addicted to it with this low margin between addiction and therapeutic use is another reason it is abused. The third reason is that you can get high from it. A number of the studies I cited in urban and suburban areas describe abuse in people who are using it to get high.

Another aspect of the abuse is that it is used both in heroin treatment clinics and informally by a number of addicts when they can't get harder drugs such as heroin. So that because it is really a narcotic and because it is so readily available, there is really no narcotic in the country that is so readily available, it is predictable that it is abused. Given the way Darvon is allowed to circulate so freely in this country, it is not in the least bit surprising.

Mr. LUKEN. Will the gentleman yield?

Mr. WAXMAN. If the gentleman will permit, I would like to complete my questions and then let the others have their turn.

Reports on Darvon deaths indicate that a majority are the results of suicide. Is this the case, and if so, how can we fault the product when its misuse is motivated by self-destructive behavior?

Dr. WOLFE. It is true that about 60 percent of the deaths are listed as suicide. That is not as high a percentage as with some other drugs such as sleeping pills, Seconal and so on, but it certainly is high. The question is, Can we do something about drug induced

suicides. The answer is "Yes." Over the last 4 or 5 years there has been a steady decrease in the total number of drug suicides mainly because of placing barbiturates in schedule II and disallowing refills. One of the easier ways of committing suicide is with drugs and if one takes that away it is very likely, according to at least a number of suicide experts, that people will not necessarily turn to another drug but may not commit suicide. As I said, a very encouraging trend is a substantial decrease in number of suicides and taking tighter action, putting tighter controls on propoxyphene might do this. We are still left with a large number of people who are unintentionally killing themselves. I think that there is responsibility to make drugs less available rather than more available to people even though they are committing suicide.

Mr. WAXMAN. How much of the abuse problem is the use of Darvon with another substance, like alcohol, that is being used in the case of a suicide attempt? In the case of inadvertent misuse by people who might not be aware of the dangers would not an educational campaign be effective in reducing deaths and injuries?

Dr. WOLFE. In a number of instances, another drug is involved although frequently the amount of the other drug in and of itself would be insufficient to cause death. The other drug is found with people who have used Darvon and there have been a number of studies showing that the other drug is not capable of causing death though with Darvon it can. The coroners generally believe it is Darvon that caused the death and not the Valium. The question is whether, through an educational campaign, you can do something about this. I am not very optimistic that during 1979, part of which there was a so-called educational campaign, according to Lilly, there really was no percentage difference in the number of people who were being seen in emergency rooms or dead in coroners' offices with Darvon who also had another drug involved.

When people become addicted, when people lose their normal mental state to euphoria or psychosis, which can be caused by Darvon or Darvocet they may not respond to an educational campaign even if the physician responds. It was clear that even the educational campaign that Lilly said they conducted didn't get this very basic kind of information across. Only 7 percent of the doctors surveyed spontaneously remembered, for example, that you should not use Darvon with alcohol. So it has not worked and I think that if we keep pretending that this kind of thing is going to suffice, we are going to see thousands of more people die and tens of thousands more come into the emergency rooms.

Mr. WAXMAN. Your first recommendation is that the drug be banned, and that even physicians who feel that this drug would be appropriate for the treatment of a patient would not be allowed to prescribe it. Is that correct?

Dr. WOLFE. That is right. We have asked repeatedly and have never gotten a satisfactory answer to the following question: Can you identify a group of patients who can: One, not use aspirin; two, not use acetaminophen, Tylenol; or three, not use codeine. Codeine is also a narcotic but it does not have as near the propensity to cause death as propoxyphene. No one has come up with an identifiable group of people who cannot use one of these three less expensive, equally or more effective and much safer drugs, so that unless

there is some need for a target population that would justify keeping the drug on the market, we don't believe it should stay on. There certainly is new information, namely the Darvon deaths and abuse, that is, the change in the safety status. It was on that basis that we sought to get it banned entirely.

Mr. WAXMAN. Since most drugs have the potential of an adverse side effect it seems to me what you are saying is that because the physicians may not be aware of the dangers with the use of Darvon that we ought not let the physician prescribe the drug. Would that not hold true for physicians prescribing other drugs that they might not be aware of the full implications? Wouldn't the answer to that be to educate physicians, because otherwise what you are suggesting is that we should not have physicians prescribe drugs?

Dr. WOLFE. Well, not quite, because most of the drugs on the market, if not all, belong on the market at least for certain kinds of indications. In only a very small number of instances have we ever asked the FDA to ban a drug. Usually this drug is excellent for a certain group of people. For this group of people the benefits clearly outweigh the disadvantages. But, as in the case of antibiotics for colds, let's stop prescribing. For Darvon though, as I mentioned, there really is not any group of people who get some advantage out of this drug who would not get an equal and greater, safer advantage out of aspirin, acetaminophen, or codeine.

Given that it is not banned, which is certainly the present status, a doctor who may, on the basis of whatever information he or she has available, think that the patient is not going to abuse it, writes a prescription for 50 Darvon; the patient goes home, uses it, notices you can get high on it or might get addicted to it without ever talking to the doctor again. The patient gets another 50, another 50, another 50, another 100 or whatever and can call in at the end of 6 months and say, "My prescription ran out and I still have pain from my back injury. Can I have some more?" This reflects the incredibly low safeguards, even given that physicians are educated. This could be an educated physician, for instance, who knew that you should not have given it to people who had alcohol or drug problems. So we think, aside from banning the drug, this is a good argument for saying no refills for Darvon.

Mr. WAXMAN. So the choice then is have the drug in schedule IV or change it to a tighter schedule. You recommend schedule II which would mean that the drug could not be prescribed over the phone and could not be refilled without a separate prescription. Am I correct in understanding that schedule IV controls permit phone prescriptions and allows prescriptions to be refilled five times within a 6-month period?

Dr. WOLFE. That is right.

Mr. WAXMAN. The doctor would still have the ability to prescribe the drug under schedule II?

Dr. WOLFE. Yes, but would have to reevaluate the patient each time. As I said, one reason for the sharp decrease in deaths from barbiturates is that the patient could not keep running off and getting refills without some reevaluation.

Mr. WAXMAN. Do you believe the difficulties you have had in putting stricter controls on propoxyphene, indicates the need for changes in the scheduling process and amendments to the Con-

trolled Substances Act? You made your petition to FDA, they listened to it, they evaluated it, they rejected it. That decision was based on existing law. Is current law adequate?

Dr. WOLFE. Before giving you my opinion I would give you the opinion of the Drug Enforcement Agency. The Justice Department in testimony in January of 1979 at the Senate hearings on propoxyphene said that they believed that as it was currently written they could not put propoxyphene on schedule II but invited a change in the law that would allow this. One of the curious facts, which I think is a fact nevertheless, is that the traditional kinds of reasons for controlling drugs in various schedules of the Controlled Substances Act has been traditional abuse such as illicit manufacturer, street sales, addiction, and so forth and that is, I think, what the law says. Things such as death per se have not been looked upon as a sufficient reason. We have both in the case of propoxyphene. One of the reasons that some of the traditional street abuse, at least the illicit sales, have not happened as much with Darvon is that it is so easily available. In our petition to DEA we focused very much on the deaths and less on the widespread evidence, which I have now begun to review this morning, of addiction and abuse.

Mr. WAXMAN. Do you have recommendations for changes in the Controlled Substances Act?

Dr. WOLFE. I think the law should be changed so that drugs such as propoxyphene could be put in schedule II. It is interesting that now the DEA, because of the international action, is going to be forced to at least put the raw material in schedule II and put production quotas on it. They have the option of putting the pills themselves in schedule II and proposing a no-refill policy. I think that if the law is written or interpreted in such a way that the agency does not think they can easily, as opposed to with difficulty, put the drug in schedule II it should be rewritten for that purpose because certainly it is the drug associated with more deaths and, in some instances, as much abuse as most other drugs, including codeine which is already in schedule II.

Mr. WAXMAN. Thank you. I know other members have questions and I don't want to take up any more time.

Dr. Carter.

Mr. CARTER. Thank you, Mr. Chairman.

Dr. Wolfe, your believe that both Darvon and codeine should be in schedule II; is that correct?

Dr. WOLFE. Schedule II, right.

Mr. CARTER. Have deaths from codeine decreased significantly since this drug was placed in schedule II, is that correct?

Dr. WOLFE. That is right.

Mr. CARTER. What about Nembutal?

Dr. WOLFE. Nembutal, I believe, is also in schedule II.

Mr. CARTER. You didn't mention that.

That is called yellow jackets? Blue heaven? What schedule is that in, please, sir?

Dr. WOLFE. That is also schedule II. I think the only barbiturate not in schedule II is phenobarbital because it is needed for epileptics.

Mr. CARTER. What is the cause of death when propoxyphene is used?

Dr. WOLFE. The pharmacologic cause of death? Is that what you mean?

Mr. CARTER. No, the physiological cause of death.

Dr. WOLFE. It is in most respects described as a classic narcotic overdose with respiratory depression, cardiac depression, cardiovascular depression. In some cases they have people survive by giving——

Mr. CARTER. By respiratory depression. We commonly see that with any opiate, correct?.

Dr. WOLFE. That is correct.

Mr. CARTER. How do you account for the diminution in the number of prescriptions written for Darvon from 37 million in 1976 to 24 million in 1979?

Dr. WOLFE. Well, I think that there is not any one answer. I will give just several. One, it was placed in schedule IV and there was a slight steady decrease associated with being placed in schedule IV but the largest decrease in any year was from the end of 1978 to the end of 1979. I think that amongst the reasons that the prescriptions fell off were our petitions, the Senate hearings, some strong statements as quoted by Mr. Waxman that were made by Secretary Califano, general increased awareness that the drug was more dangerous than people thought and perhaps less effective than people thought. So that there is no question that there has been an acceleration but we are still left with almost 25 million prescriptions in 1979.

Mr. CARTER. You mean deceleration instead of acceleration.

Dr. WOLFE. There has been a decrease. What I meant was an acceleration in how fast the prescriptions were going down during the last year. But even if it continues at that rate and no faster, we are still going to have large numbers of people using the drug, abusing the drug, getting killed with it so really what I am suggesting by doing something more than what has been done is to figure out how we can bring the drug to a quick demise instead of people that are using it.

Mr. CARTER. Is the narcotic antagonist Narcan as effective against propoxyphene as it is against heroin?

Dr. WOLFE.I have just recently spoken to some people in Dallas at the University of Texas who have conducted quite a careful study of that and they find that in a number, a third, a half of the people who are still alive when they came to the emergency room, they were able to revive them, resuscitate them with Narcan. In others they were not. One reason may be that Darvon, as you know, is metabolized into another drug and Narcan only antagonizes the parent drug, the drug that is given. Once it is metabolized into the other form, that aspect of it cannot be antagonized by Narcan and it may be that because someone who has been using it for a long time has built up enough of the byproduct which also has toxic properties that they don't respond. Those are the kinds of things that they are trying to sort out in this Dallas study now.

Mr. CARTER. What is the difference, Doctor, as you see it, between Darvon and Darvon-N?

Dr. WOLFE. Well, when the patent ran out for propoxyphene or Darvon hydrochloride, the company came up with a new form of it, a new salt called the napsylate salt, more slowly absorbed. That is

one of the main characteristics. It takes a longer time to reach a particular blood level than the hydrochloride. I don't believe there is much difference as far as abuse or deaths. It might well be that the hydrochloride, because it reaches a higher level sooner, might be more dangerous but I don't think that there is really good information on that. I think the main difference is that it is more slowly absorbed. The most commonly used form now is neither of those but Darvocet-N, propoxyphene combined with acetaminophen. This accounts for the lion's share of the sales by Lilly, having replaced Darvon compound which used to be the biggest seller.

Mr. CARTER. It does endanger or does cause difficulties with the kidneys.

Dr. WOLFE. It does, but I think there is very good evidence for that, too. In most of the Darvon deaths though the death is attributed to the Darvon.

Mr. CARTER. You would like to see Darvon banned completely as heroin is; is that correct? That is what you suggest?

Dr. WOLFE. Yes; that is correct, I would like to see it banned completely.

Mr. CARTER. You would not want it even to be placed in schedule II?

Dr. WOLFE. Well, we have said, as we did in November 1978 when we petitioned, that it either should be banned or put in schedule II as a less satisfactory but better than what we have now, fallback position. Putting it in schedule II would at least reduce substantially the amount of prescriptions filled as a result of not allowing refills.

Mr. CARTER. It is rather unusual. As a physician I don't believe I have ever had a patient ask me for Darvon.

Dr. WOLFE. That makes your practice sound like a very good one, I think.

Mr. CARTER. Sometimes we can have serious difficulties. Do you suggest placing it in schedule I with LSD or a ban by removing its new drug application?

Dr. WOLFE. Well, schedule I is reserved, as you know, for drugs which do not have an approved medical use.

It would be the banning process that would go through FDA, not through the Drug Enforcement Agency. We would be saying we believe that the risks so outweigh the benefits that it should be taken off the market. It would just be banned as an imminent danger since we believe it clearly is an imminent danger to the public.

Mr. CARTER. Thank you, Doctor, for your excellent statement.

There is one other thing I want to say. I had a sad experience one time when I was practicing. An older doctor died and left me a patient who had an amputation of his left leg. This man was an addict and a time or two I prescribed a narcotic for him, as I was permitted to do, but it was contrary to my ethical belief to continue. When I did discontinue this drug, he hanged himself from a bridge.

Thank you.

Mr. WAXMAN. Thank you, Dr. Carter.

Mr. Leland.

Mr. LELAND. No questions.

Mr. WAXMAN. Mr. Luken.

Mr. LUKEN. Doctor, just a question or two.

You really did mention methadone or Darvon in the same breath with methadone.

Dr. WOLFE. Yes.

Mr. LUKEN. Did you say they are comparable? In what respect?

Dr. WOLFE. Two major respects. One, if you look at their chemical construction, they are very much the same. There are only a couple parts of the molecule that are different. They are both sold by Lilly. A third similarity is that they are both used, Darvon more in southern California, in drug treatment programs to treat heroin addicts.

Mr. LUKEN. Darvon is used as a substitute?

Dr. WOLFE. Yes, Darvon is used in southern California, in the Los Angeles area, in at least two large drug treatment programs to treat heroin addicts instead of methadone and one reason cited by the people who use it is that it is more available.

Mr. LUKEN. But it is not used generally throughout the country. Isn't methadone still used?

Dr. WOLFE. Yes, that is used also. Darvon is used in some places.

Mr. LUKEN. Methadone is much more—I cannot get into the jargon with you but it is much stronger, isn't it, closer to heroin?

Dr. WOLFE. I think stronger is a good description but qualitatively they have very similar problems.

Mr. LUKEN. It would be a choice for the heroin user?

Dr. WOLFE. In southern California they are using Darvon over methadone.

Mr. LUKEN. Would the user choose it?

Dr. WOLFE. That I can't answer. In the testimony I mentioned that——

Mr. LUKEN. I mean with Darvon being so readily available, if the heroin user really preferred it, he would not go to the methadone clinic, would he?

Dr. WOLFE. Yes, he would. As I mentioned on page 6 of the testimony, several methadone clinics have reported significant use of propoxyphene. In New Orleans it was found in 61 percent of the urines of people coming into their clinic so that suggests that it is available and they use it.

Mr. LUKEN. Don't drug addicts tend to turn to anything almost in desperation? Do they just turn to Darvon?

Dr. WOLFE. I think you are right, they do turn to other things, but of the other things that they can easily obtain the one that is a narcotic is Darvon. Darvon is the only easily accessible narcotic in the country.

Mr. LUKEN. Are there any statistics on Darvon addiction?

Dr. WOLFE. There are a number of studies reporting Darvon addiction. That is only one of the problems though. Before it was marketed it was studied in Lexington in the Federal Addiction Research Center and it was shown that it could partially suppress the addiction due to morphine and that it in and of itself was addicting. There are some studies in controlled circumstances where they will take a bunch of people, give them a certain amount of Darvon—they have done this down at Lexington, too—and when they were withdrawn off the drug, the withdrawal is

mild, not as severe as heroin or morphine but there is a mild discernible drug withdrawal syndrome.

Mr. LUKEN. No one has quantified the number of people?

Dr. WOLFE. No, no one has quantified the number of people in the country but one thing we are very concerned about is the FDA study which I mentioned on the bottom of page 4 which shows that there are 72,000 people in this country who are getting enough Darvon because of the refill policy to take more than twice the recommended dose, which is an amount that has been shown to be addictive. Now obviously every one of these people is not addicted but if they wanted to they could be. It is so easily available that they are able to take that much.

Mr. LUKEN. If there is any addiction, you would not say it is common?

Dr. WOLFE. I just don't know. That is just one of the forms of abuse. I have said in these studies in Philadelphia, the ghetto, and suburban areas getting high is the different way of using the drug as distinct from addiction.

Mr. CARTER. Would the gentleman yield?

Mr. LUKEN. I be glad to yield to the gentleman from Kentucky.

Mr. CARTER. I thank the gentleman for yielding. Is it true that there are fewer deaths from Darvon and so it is presently the treatment of choice of some physicians in treating drug addiction because of that fact?

Dr. WOLFE. It is absorbed more slowly. It really is difficult to tell from the data whether it is associated more often or less often than the other kinds of Darvon with deaths. The third thing you mentioned, it is true, the napoylate salt is the treatment of choice for treating addicts.

Mr. CARTER. Why would that be?

Dr. WOLFE. It may be because of its slow absorption. Theoretically what you are saying makes sense that because you don't get as high a blood level as quickly it might be less dangerous. When the coroners collect causes of death, they don't get accurate data on which kind of Darvon was used.

Mr. CARTER. I thank the gentleman for yielding.

Mr. LUKEN. In reference to deaths you used the figure of Darvon. Those are Darvon related deaths, right?

Dr. WOLFE. That is right.

Mr. LUKEN. Darvon was mentioned in effect.

Dr. WOLFE. Yes. That breaks down in two ways. For propoxyphene, 92 percent of them according to the people who collected data were drug induced and 8 percent were drug related. Drug induced means a high enough level was there, drug related means the drug was there.

Mr. LUKEN. It would not be solely Darvon drug?

Dr. WOLFE. In about a quarter of the cases there is no other drug around so that for those it is, for all practical purposes, Darvon. In the other cases there are other drugs around but in discussing this with the coroners, in most cases, even though there are other drugs around, there are drugs such as aspirin in many cases, alcohol which can combine and make for a worsening, Valium which in and of itself is not dangerous enough. For the most part the coroners that are reporting these cases would tell you that the over-

whelming proportion of these deaths really were caused by Darvon, not just related to its use.

Mr. LUKEN. In those cases would the coroner also say that they involved more than the quantities or therapeutic quantities that were ingested? They were overdoses?

Dr. WOLFE. Absolutely. As I said, what we are talking about is the drug which, because of its properties, is addicting, and euphoria-producing. Some people tend to use more than they are supposed to and the route to abuse is very easy because of those problems.

Mr. LUKEN. Then there would be a suicidal factor?

Dr. WOLFE. In some cases there would be a suicide and in some cases an accident.

Mr. LUKEN. Do you have any statistics on that? Isn't the overwhelming majority of the cases suicidal or emotional problems rather than accidental?

Dr. WOLFE. Well, you are correct.

Mr. LUKEN. I am not sure where that leads us.

Dr. WOLFE. About 50 or 60 percent of the cases are listed as suicidal and the others are accidental, people who may have been abusing the drug but were not intending, as best as one can tell to commit suicide. Just by way of example, this drug abuse warning system that we talked about only covers a third of the country. In Ohio, for example, the only city that is covered is Cleveland where I am from. Cincinnati is not covered.

Mr. LUKEN. The statistics are obviously faulty.

Dr. WOLFE. That is right. I therefore called the Cincinnati coroner's office to find out what some of their experiences had been and, in 1978, for example, they reported that there have been 10 Darvon abuse deaths. These are not suicide deaths but abuse deaths, ones where there is no evidence that the person was intending to commit suicide. In two of them there was only Darvon found. In others there was aspirin in one and alcohol in another. This is a problem even in Cincinnati where you are from and it is found in both suicide and accidental situations in that city.

Mr. LUKEN. You have been doing research on me in Cincinnati. I am going to stop asking questions.

Dr. WOLFE. Not on you.

Mr. LUKEN. Thank you, Mr. Chairman.

Mr. WAXMAN. Thank you, Mr. Luken.

Mr. Dannemeyer.

Mr. DANNEMEYER. Thank you, Mr. Chairman.

If you say this is no more effective than aspirin, why do you think doctors continue to permit it to be used by their patients?

Dr. WOLFE. Well, even the company that makes it, I don't know that they will restate it this morning, they don't believe that the Darvon alone is any more effective than aspirin. That is not the dispute.

The other point you raise is very good. Why, if that is the case, do they prescribe it? I think there are at least two answers. One is that the act of prescribing a drug imparts a certain air of—it is better than if you just told someone to go to the drugstore and take aspirin. A practicing internist testified at the Senate hearings last year specifically on that point and he said that he would rather

spend an extra few minutes telling the patient, "I would not give you Darvon, aspirin is safer, it is less expensive," and convince the patient, using the powers of persuasion that a physician has, that even though aspirin is not a prescription drug it is as good. A lot of doctors won't want to take the time to do that. I think that is one reason.

Another reason is that it is very heavily advertised. Doctors certainly do, amongst other things, respond to drug advertising.

Another reason is that when it first came on the market in 1957 it was heavily promoted as being as effective as codeine, as being a nonnarcotic and being nonaddictive. All three of those statements turn out to be false but the doctors get into various kinds of prescribing habits and sometimes it takes more than what has been done thus far to wrench them out of those habits.

Mr. DANNEMEYER. Are you suggesting that, when prescribing Darvon, the doctor has a thought that somehow his advice may be appreciated more by the patient if it calls for a drug that requires a prescription rather than just an ordinary aspirin that the patient may wander into the drugstore and bought on his own?

Dr. WOLFE. Yes, and Dr. Lasagna who testified before the hearings last year said pretty much the same thing. The placebo effect, as imparted by the physician, is a form of the laying on of the hands but unfortunately unlike a real placebo, a sugar pill, Darvon is not safe! The placebo process that you just described, particularly for something like pain, has an effect. When these pain drugs are studied, they are studied opposite a sugar pill and if you just look at the people who got the sugar pill alone some 30 or 40 percent get relief from it because they believe it will work. The brain is capable of producing some chemicals that have a pain killing effect.

Mr. DANNEMEYER. This Health Research Group, is it incorporated?

Dr. WOLFE. Yes.

Mr. DANNEMEYER. Where?

Dr. WOLFE. Washington D.C.

Mr. DANNEMEYER. When?

Dr. WOLFE. In 1971.

Mr. DANNEMEYER. How many members on the board of directors does it have?

Dr. WOLFE. Four, I believe.

Mr. DANNEMEYER. You are one of the four?

Dr. WOLFE. No, I am not. I am just an employee.

Mr. DANNEMEYER. How long have you been associated with this entity?

Dr. WOLFE. Since it started.

Mr. DANNEMEYER. These four members of the board of directors, are they elected?

Dr. WOLFE. No.

Mr. DANNEMEYER. How long have the existing four members of the board held those offices?

Dr. WOLFE. I really don't know that information, I could get it for you.

Mr. DANNEMEYER. Approximately, from the inception of this organization?

Dr. WOLFE. I really don't know. As I said, I will be glad to get
u the information.
Mr. DANNEMEYER. Are these residents of the District of
olumbia?
Dr. WOLFE. I think two of them are.
Mr. DANNEMEYER. Do you know where the other two come from?
Dr. WOLFE. One is from Michigan.
Mr. DANNEMEYER. The other one?
Dr. WOLFE. I really don't know.
Mr. DANNEMEYER. Are they physicians?
Dr. WOLFE. One of them is a physician, two are attorneys, one of
em is Mr. Nader.
Mr. DANNEMEYER. Mr. Nader.
Dr. WOLFE. Yes.
Mr. DANNEMEYER. His first name is Ralph?
Dr. WOLFE. That is the one.
Mr. DANNEMEYER. Are they compensated for their services?
Dr. WOLFE. Again, I don't know. I think they are not but I could
wrong.
Mr. DANNEMEYER. When is the last time the board met?
Dr. WOLFE. Sometime probably in the last several months.
Mr. DANNEMEYER. Were you present at the meeting?
Dr. WOLFE. No, because I am not a member of the board.
Mr. DANNEMEYER. When was the last time you attended a meet-
g of the association?
Dr. WOLFE. I am simply an employee and employees can but
n't attend these meetings. I certainly could if I wanted to.
Mr. DANNEMEYER. Who in the organization undertook to ask you
bring to our attention the evils of this drug?
Dr. WOLFE. Well, I more or less asked myself to do it. It is a drug
at I have been aware of for a long time. It came on the market
st slightly before I started medical school in 1960. I was always
ncerned with what appeared to be a very effective drug and I
creasingly became aware that, not only was it not that effective,
t it was dangerous. Finally I concluded that it was time to try to
something about it. That was a couple years ago now.
Mr. DANNEMEYER. Is this a full time job for you?
Dr. WOLFE. It is, it is the only work I do.
Mr. DANNEMEYER. Thank you.
Mr. WAXMAN. Thank you, Mr. Dannemeyer. Ms. Mikulski.
Ms. MIKULSKI. You talk about Darvon's effect and abuse in terms
adolescence and on page 10 you talked about its impact on black
ople. In your statistical accumulation have you done anything in
rms of its effect on women? In other words, do women get more
arvon than men and among women who are addicted to Darvon,
ve there been more abuses or deaths in this area?
Dr. WOLFE. Well, in general women get more of most kinds of
ugs and the same is true with Darvon. A very large proportion,
mewhere around two-thirds of the deaths and emergency room
sits for this drug, are in women. So that is another group of
ople who I think have become victims.
Ms. MIKULSKI. Two-thirds of the emergency room visits and
aths are women?

Dr. WOLFE. Yes. For 1978, the last year we have complete data on, 70 percent of emergency room visits were for women and 58 percent of the deaths were for women. So both are around two-thirds.

Ms. MIKULSKI. In terms of corrective actions on this and perhaps some of the other drugs that we know can either be addictive or inadvertently cause death when taken with alcohol, do you find an effective technique is the labeling that occurs at the retail dispensing—so when you get your little drug it says, "Watch out, don't drink and drive" or anything like that? Do you think that is an effective technique in terms of consumer education and would prevent either death or mixing it with other substances that could cause dangerous reactions?

Dr. WOLFE. Well, patient package information has been used for birth control pills, for progestogens, drugs that have been used on pregnant women which have caused birth defects, and estrogens. It has been useful in those circumstances because what it has done, among other things, is give more information in the case of all three drugs than the women had before and I think it has been one factor in a decrease in the use of those three kinds of drugs. We then get into the category of drugs where the users may be addicted already either to the drug and/or to alcohol where they may be using them to get high. I don't think that this patient information approach, even if it were done, would work.

There is some indication from talking to a number of pharmacists that a lot of pharmacists don't even want to get out this little sheet that they have worked up for Darvon, they don't have to because it is a voluntary kind of program. I would suggest that even if all of them were given out that might have some slight effect but it would have nowhere near the effect that banning obviously would have or even disallowing refills because it is the refilling of prescriptions that seems to be associated with the people who are able to get enough Darvon, over 360 pills a month, so they could become addicted.

Ms. MIKULSKI. I am concerned about the innocent victims where somebody has a back pain or falls on their foot. They might go through a brief situation where they start on Valium. I would like to view this hearing as not only targeted at the Darvon issue but also other drugs that tend to be almost a popular drug that is used. I think when people start out, they take their first Valium because of a terrible problem, and don't know that it is addictive. They don't know that they have to be careful with alcoholism or any variety of other things. I'm talking in terms of the layman, not about the person who is already an addict or addicted to anything.

Dr. WOLFE. Well, two things on that point. One, for the person who didn't know, the labeling might serve as a warning but coupled with that I think not only for Darvon but for a number of other drugs, and Valium certainly comes to mind, would be seriously addressing this question of refills. If there is such a possibility of addiction in the case of Darvon and Valium or death in the case of Darvon, why shouldn't the person need to be reevaluated if it is believed that a refill is indicated? I think that by not having to go back for reevaluation and allowing the person to go back five times in the 6-month period which you can do with either Valium or

von, that is one of the things in addition to perhaps the lack of rmation on the part of the patients that sort of perpetuates the se. So that both things need to be done. In the case of Darvon her has been done for all practical purposes.

Is. MIKULSKI. I have just one final question but it is a broad one. n very much concerned about what I call the prescription uced junkies in this country and they do tend to be women. nehow or another we get more drugs. We get more drugs that either addictive or dangerous to us. I am just trying to arrive ertain conclusions. I don't want to be chasing the drug a month ry to deal with this. I just wonder what broad or specific policy ommendations would you have in this area to deal with what I sider the overprescription or overmedication of certain kinds of gs in our population, whether they are to men or women. What ut medical schools? What about pharmaceutical manufactur- ? What about labeling? We cannot go around banning every- ng. Many of these medications have useful functions.

r. WOLFE. I agree. Darvon, I don't think is one. Generally, one he kinds of the things that happens which starts people toward ng prescription junkies happens in the hospital. In some obstet- l services it is routine to write an order for a tranquilizer such Valium. Many women come in to deliver a baby and, boom, the mp is placed on their order sheet and they get a prescription for ranquilizer.

Is. MIKULSKI. Why?

r. WOLFE. Because it is assumed by the physicians that the men are going to be anxious and upset, and it might even cause ne problems with the staff, so the easiest way is to anticipate t every woman who is going to have a child is going to get upset l be given a tranquilizer. That does not happen in every hospital surveys have been done by national organizations and in a mber of hospitals, that kind of thing is close to if not routine. So tiating people in the hospital, whether it is on obstetrical serv- s or other parts of the hospital, to Valium or anything else is nething that really should be looked at seriously. Certainly one the things that Dr. Goyan has done when he was a dean of armacy was to go into the hospitals and start trying to interfere h these kinds of practices. The more of that, the better.

o that is one thing that can be done.

Another thing that can be done is, I think, in the public hool——

Ms. MIKULSKI. Wait. In terms of the Federal Government I can't tate curriculum or tell deans of pharmaceutical schools what to What would be done federally?

Dr. WOLFE. Under the professional standards review program, e program which reviews medical care in hospitals on medicare d medicaid patients, which covers most hospitals in the country, e of the things they can do in some cases is review prescribing in e hospital. I believe that if this were done for painkillers in all spitals that get medicare and medicaid patients, most hospitals the country, it is within the power of PSRO's that would set ndards to stop it. That is just one suggestion.

Mr. CARTER. Would the gentlelady yield?

Ms. MIKULSKI. Yes. Happy to yield.

Mr. CARTER. I thank the gentlelady for yielding.

This is the first time that I ever heard of Valium being given to a pregnant woman. For many women, this is not a difficult time at all, it is one of the most beautiful parts of her life. Nothing is more beautiful than a pregnant woman. It has not been my experience that they prescribe Valium in every case.

Dr. WOLFE. In some hospitals they do and in some they don't.

Mr. CARTER. I would just like to see some proof that they do that regularly because it is inconceivable to me.

Dr. WOLFE. There is a study done by the group in Ann Arbor and they found that in a number of hospitals on the OB service they were routinely or almost routinely prescribing this drug. In many other hospitals they were not, but in virtually all the hospitals at least a proportion of women were getting tranquilizers on the OB service. As you said, for most women it should be and is a very happy time, and I don't see any reason either medically, ethically, or morally why this kind of thing should happen but it has.

Mr. CARTER. I thank the gentlelady for yielding.

Ms. MIKULSKI. If I could just summarize the point you made, what you are recommending is that an appropriate function of the review process in reviewing medicaid, medicare patients which we pay for would be to look at unnecessary or excessive over medication or prescription in tranquilizers and painkillers the same way as we would monitor for unnecessary surgery.

Dr. WOLFE. That is absolutely correct.

Ms. MIKULSKI. Thank you.

Thank you, Mr. Chairman.

Mr. WAXMAN. Mr. Lee.

Mr. LEE. Thank you, Mr. Chairman.

Mr. Wolfe, if one looks at the conclusions of 1978 and to read your statement this morning and listen carefully to your verbal presentation, is it fair to characterize the conclusion by saying that you are recommending the same thing today that you were 2 years ago?

Dr. WOLFE. That is correct except that one of the things that we had asked for 2 years ago has been done. We had suggested or petitioned for this drug being put in schedule II which would have imposed production quotas and a no-refill policy. There are now production quotas as a result of international action to place this drug in international schedule II so there has been some progress but it has just happened in the last few weeks.

Mr. LEE. Do you recognize that we have made progress in the educational aspects or the informational aspects in terms of distributing the information to the public?

Dr. WOLFE. I believe that as a result of congressional hearings, our petitions, and other activities, not so much as a result of Lilly's educational campaign, there are more people aware of the dangers of the drug and the main indication of that is there has been the largest fall in prescribing in the last year. But it still leaves us with 25 million prescriptions of the drug, which is a large number.

Mr. LEE. Would you not agree with the reduced death rates of Darvon that we are on the right track?

Dr. WOLFE. We are going in the right direction, there is no question about that. I just don't think we are going fast enough. If

ve continue on the track at this present pace, we are going to lose nother 5,000 or 10,000 people. Really what I am asking for is ctions that might much more rapidly do away with the prescrib- ng of Darvon, either by banning or put——

Mr. LEE. Have you read Dr. Goyan's testimony?

Dr. WOLFE. No, I have not.

Mr. LEE. One of the things they have referenced has been a ignificant decrease in the death rate in the last 2 years.

Dr. WOLFE. I am also pleased. I don't think we disagree. It is a natter of whether we could have moved more quickly as happened vith barbiturates and so forth. Any time that there is a decreased umber of deaths or emergency room visits I am pleased but I am ery concerned that we are still going to have for 1979, about 1,000 leaths in the country and that is unconscionable considering how iseless the drug is.

Mr. LEE. Those 1,000 deaths are purported deaths, not——

Dr. WOLFE. Those are the medical examiner's findings of people vho died who had Darvon in very high concentrations.

Mr. LEE. Or in combination.

Dr. WOLFE. That is the system we use. It is a lot of deaths.

Mr. LEE. Thank you, Mr. Chairman.

Mr. WAXMAN. Mr. Walgren.

Mr. WALGREN. Just briefly, Dr. Wolfe. I am coming in the middle f this. What is the difference between schedule IV and schedule I and what is left in terms of control that would come from the chedule II classification?

Dr. WOLFE. schedule IV in terms of the interaction between the loctor and the patient and the manufacturer, it really involves a imit of five refills in a 6-month period after a prescription is vritten. It allows phone prescription. So if you go to a doctor and he doctor is unwise enough to prescribe Darvon, you get a pre- cription for 50 or 100 pills, you can go on without seeing the loctor from what was the original phone prescription and get more Darvon. There are no production quotas.

Schedule II, on the other hand, imposes production quotas which are now going to be forced on the United States as a result of the nternational schedulings but also disallows a refill and it is that aspect, in addition to just having production quotas on it, that we hink would be very important if it is decided that the drug is not going to be banned, because as mentioned on the bottom of page 4 of the testimony there are a lot of people in this country—72,000— who are getting enough Darvon, largely as a result of refills, to be able to take more than an amount which has been shown to be addictive, so mainly schedule II is production quotas and a no-refill policy.

Mr. WALGREN. Is there any outline comparison that you can make of other drugs under schedule II as compared to Darvon in terms of the appropriateness of classifying the Darvon schedule II?

Dr. WOLFE. Well, the one that is in the same pharmacologic category as Darvon is codeine. In the international schedule II, essentially all of the drugs before Darvon was put in there, were codeine and codeine-like compounds, but codeine alone is in sched- ule II and combinations of codeine are in other schedules. It is said by people who have studied the two drugs in terms of the compari-

son of their abuse that in many respects codeine and Darvon are the same. When Darvon was put in schedule II internationally it was said to have harm similar to the other drugs in that schedule. On the bottom of page 9 I mention the fact that the death rate per million prescriptions for Darvon is actually almost four times higher than for codeine and for other evidences of abuse it is about the same, maybe slightly higher for Darvon. But certainly, in terms of that drug (codeine) which is in schedule II, as far as the pills alone, Darvon is very comparable, if not worse, as far as evidence of abuse.

Mr. WALGREN. Does it not have a no-refill policy?

Dr. WOLFE. That is correct. The reason for that is in a number of countries the drugs that are in schedule II are not prescription drugs and therefore when something is put in international schedule II there can't be an element of schedule II that speaks to prescription limits because, as I said, in a number of countries they would not have the legal authority to impose that. Schedule II, there are a number of recordkeeping requirements, export-import requirements, but the main thing is that it requires all 110 countries who signed that international convention to put production quotas on the drug.

Mr. WALGREN. Was the manufacturer of the drug engaged in an educational campaign on its dangers at the same time it was giving out free samples to those who would prescribe it?

Dr. WOLFE. That is what appears to be the case from the information that the FDA collected on the way the drug was being detailed and so forth. They found that in more than three-quarters of the cases, in October and November, free samples had been given out. More importantly than that is the inadequacy of the educational part. I mentioned in a memo that someone who studied the educational campaign found that only 7 percent of the doctors spontaneously recalled the fact that Darvon and alcohol were sort of a no-no, so aside from the promotional aspects of it, which are cause enough for concern, the educational aspects don't appear to have been very effective according to the FDA, which sent a letter to Lilly criticizing them for the program.

Mr. WALGREN. Thank you, Mr. Chairman.

Mr. WAXMAN. Dr. Wolfe, I thank you for your testimony. You have generated a good bit of interest and taken up more time than I anticipated. We appreciate your being with us.

[Testimony resumes on p. 78.]

[The following material was subsequently received and included in the record at the instruction of the chairman:]

Public Citizen

June 30, 1980

Patricia Harris, Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Harris,

The Health Research Group is submitting today to the Drug Enforcement Administration (DEA) the enclosed petition. It requests the immediate transfer of all propoxyphene-containing products from Controlled Substances Schedule IV to Schedule II as agents which demonstrate considerable addiction potential, abuse liability, and human toxicity, and which have limited therapeutic usefulness. Since refills (approximately 50% of Darvon sales) are an essential factor in supporting the abuse of these drugs, putting all propoxyphene products in Schedule II--thereby disallowing refills--will greatly reduce the numbers of injuries and deaths predictably associated with the easy availability of these drugs.

On April 24 of this year, we wrote to you concerning the United Nations action 1/ to place propoxyphene (the active ingredient in Darvon) in International Narcotics Schedule II. To comply with this change in international classification, the DEA has confirmed that there are several options, ranging from the imposition of production quotas on propoxyphene to placing all Darvon-containing products in U.S. Controlled Substances Schedule II. This latter option would add an important "no refill" policy to the production quota control.

Although we still favor banning these not terribly useful but extremely dangerous drugs, full Schedule II controls for all propoxyphene-containing products would greatly reduce their use and abuse for the following reasons:

1/ The U.N. ruling is binding in the U.S. and 109 other countries which are signatories of the 1961 Drug Convention.

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1. According to the latest prescription marketing data,[2] almost 50% of propoxyphene prescriptions filled are refills. Given the ready accessibility of these drugs, with lax Schedule IV controls allowing up to 5 refills within 6 months of the original prescription without contacting the physician, the number of potential misusers of propoxyphene products is quite large.

2. A recent FDA-sponsored study[3] found significant over-acquisition of propoxyphene products via refills. Of the 11.6 million national propoxyphene users during February-November 1978:

- 426,000 people had their prescriptions refilled at a rate that enabled them to consume over 180 pills a month, or more than the recommended daily dose of 6 per day.

- 72,420 people obtained, via refills, over 360 pills a month or more than twice the maximum recommended daily dose of 6 per day--an amount sufficient to cause addiction when used regularly.[4] Commenting on this subgroup the authors stated:

  "If the propoxyphene was consumed according to the prescription refill records, their daily consumption could have averaged 12 or more dosage units. Considering that dependence may occur if patients take as few as 8-12 dosage units per day, the implications are obvious."

3. Given propoxyphene's addiction liability at amounts only slightly above the recommended dose and its euphoria-producing and weak pain-relieving properties--all documented in the enclosed petition--it is not surprising that easy availability of these drugs has led to such massive abuse, as evidenced by addiction, emergency room episodes, and deaths.

2/ National Prescription Audit, Therapeutic Category Report, IMS America, Ambler, Pa., 1979.

3/ Kennedy, D.L. and Burke, L.B., "Propoxyphene: An Example of the Need for Increased Pharmacist/Patient Interaction, Amer. Pharm., NS19:45-46, 1979.

4/ FDA Drug Bulletin, February-March 1979, p. 2.

4. There is a close correlation between the amount of propoxyphene prescribed and the amount abused. Between 1976-1979, prescriptions fell 33% while emergency room mentions experienced a 29% decrease. With almost 50% of prescriptions being refills, eliminating this too easily obtainable source of propoxyphene would have a profound effect on use and abuse.

5. In a recent appraisal of efforts by Eli Lilly and Company to sensitize physicians and patients to the dangers of propoxyphene products, FDA Director J. Richard Crout characterized Lilly's "educational campaign" as a "standard promotional campaign." Since it is highly unlikely that Lilly will voluntarily "do in" this profitable drug, Schedule II controls are warranted.

During the May 21, 1980 House Health Subcommittee Hearings on propoxyphene, FDA Commissioner Jere Goyan indicated that your department was considering recommending placement of all propoxyphene-containing products into Schedule II or urging doctors to write "no refills" on all prescriptions for propoxyphene products amongst the options for regulatory action on these drugs.

Since the Controlled Substances Act requires that the Secretary of HHS submit an opinion to the Department of Justice concerning any proposed scheduling or rescheduling of drugs, we urge you to support our petition and recommend the immediate reclassification of all propoxyphene-containing products under U.S. Schedule II as a means to curb the use and abuse of these dangerous drugs.

Sincerely,

Sidney M. Wolfe, M.D.
Director

Pauline Sobel
Scientific Research Assistant

Enclosure

cc: Dr. J. Richard Crout, Director,
FDA Bureau of Drugs
Dr. Jere E. Goyan, Commissioner
Food and Drug Administration
Hon. Henry A. Waxman, Chairman,
Subcommittee on Health and the
Environment

Public Citizen

June 30, 1980

Benjamin R. Civiletti, Attorney General
United States Department of Justice
10th & Pennsylvania Avenues, N.W.
Washington, D.C. 20530

Dear Mr. Civiletti,

The Health Research Group is submitting today to the Drug Enforcement Administration (DEA) the enclosed petition. It requests the immediate transfer of all propoxyphene-containing products from Controlled Substances Schedule IV to Schedule II as agents which demonstrate considerable addiction potential, abuse liability, and human toxicity, and which have limited therapeutic usefulness. Since refills (approximately 50% of Darvon sales) are an essential factor in supporting the abuse of these drugs, putting all propoxyphene products in Schedule II--thereby disallowing refills--will greatly reduce the numbers of injuries and deaths predictably associated with the easy availability of these drugs.

On April 24 of this year, we wrote Department of Health and Human Services (HHS) Secretary Patricia Harris concerning the United Nations action[1/] to place propoxyphene (the active ingredient in Darvon) in International Narcotics Schedule II. To comply with this change in international classification, the DEA has confirmed that there are several options, ranging from the imposition of production quotas on propoxyphene to placing all Darvon-containing products in U.S. Controlled Substances Schedule II. This latter option would add an important "no refill" policy to the production quota control.

Although we still favor banning these not terribly useful but extremely dangerous drugs, full Schedule II controls for all propoxyphene-containing products would greatly reduce their use and abuse for the following reasons:

1/ The U.N. ruling is binding in the U.S. and 109 other countries which are signatories of the 1961 Drug Convention.

PUBLIC CITIZEN HEALTH RESEARCH GROUP • 2000 P Street, NW • Washington, D.C. 20036 • 202/872-0320

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The Health Research Group urges you to support our petition and take the strongest measures possible to curb the use and abuse of these dangerous drugs by reclassifying all propoxyphene-containing products in U.S. Schedule II.

Sincerely,

Sidney M. Wolfe, M.D.
Director

Pauline Sobel
Scientific Research Assistant

Enclosure

cc: Peter Bensinger, Administrator
Drug Enforcement Administration
Department of Justice

Sidney M. Wolfe, M.D. and)
)
Public Citizen Health)
Research Group)

Petitioners

TO: Honorable Benjamin R. Civiletti
Attorney General of the United States; and

Honorable Peter Bensinger, Administrator
Drug Enforcement Administration, Department of Justice

PETITION REQUESTING THE TRANSFER OF ALL PROPOXYPHENE-CONTAINING PRODUCTS FROM CONTROLLED SUBSTANCES SCHEDULE IV TO SCHEDULE II

CITIZEN PETITION

In light of the recent United Nations decision to place propoxyphene (PX) in International Narcotics Schedule II, the Health Research Group (HRG) urges the Drug Enforcement Administration (DEA) to take immediate regulatory action and reclassify all PX-containing products under the Schedule II regime.

The Controlled Substances Act mandates that a drug may be classed in Schedule II if it has "a high potential for abuse" and it leads to "severe psychological or physical dependence."[1] The petitioners contend that there is overwhelming evidence that PX-containing products fulfill these criteria. A review of the pertinent literature provides sufficient proof of abuse potential and addiction liability to warrant rescheduling of all PX-containing products. Anything less than Schedule II will not result in the decrease in prescriptions necessary to curb abuse.

The petitioners submit this petition under the Controlled Substances Act, 21 U.S.C. § 811(a), and the Administrative Procedure Act, 5 U.S.C. § 553(e).

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STATEMENT OF GROUNDS

INTRODUCTION

Propoxyphene (PX), a narcotic that induces the classic triad of psychological dependence, physical dependence and tolerance, has repeatedly been shown in controlled clinical trials to provide an analgesic effect somewhere between that of a placebo and 2 aspirin. Because it is so commonly prescribed and because toxicity develops only slightly above the recommended daily dose--especially in combination with alcohol and other central nervous system depressants--PX is implicated in more deaths each year than any other prescription drug. Moreover, there is recent evidence that PX is an object of dangerous abuse by growing numbers of people. All these factors weigh heavily toward the imposition of more stringent controls.

In November 1978, HRG proposed altering PX's regulatory status in either of two ways: HRG petitioned the Department of Health, Education and Welfare (HEW) to ban the drug as an "imminent hazard," and simultaneously asked the DEA, as an alternative, to tighten restrictions on the drug's use by placing it in Schedule II. A key factor in the HEW decision to reject the HRG proposals was Eli Lilly's commitment to an "educational program" intended to sensitize prescribers and patients to the hazards of PX products. In a recent HEW appraisal of Lilly's efforts, the following was reported:

> "Lilly has not conducted its campaign to prescribers as FDA had expected. Detail persons visiting physicians failed to emphasize the user warnings in the majority of visits, left samples of Darvon in 50-75% of visits, and on the average spent less than half of the time on Darvon during the visits."[2]

The "abuse of propoxyphene appears to be directly related to the relative ease with which this drug is obtained from physicians,"[3] yet "the Darvon educational campaign has not been shown to have had an important impact into physician decision-making."[4] Since abuse is abetted by availability, only when the Justice Department transfers all PX-containing products to Schedule II--thereby limiting production and making the drugs ineligible for multiple refills and telephone prescriptions--will the misuse of these minimally effective, highly toxic, and widely abused drugs be mitigated.

I. Properties of Propoxyphene Lead to Abuse, Including Death

A. Availability

Easy availability of PX fosters abuse. According to Maletsky, "physicians will unknowingly initiate and maintain a PX addiction."[5] In its March 20, 1979 report to the FDA, the DEA states:

> "It seems that the major source of supply for propoxyphene is the unwary physician who is ignorant to the abuse/addiction liability of the drug or is not aware of the patient's intent for abuse."[6]

Thus, it is not difficult to find obliging physicians or pharmacists to cater to patients' demands for more PX. Lilly has claimed that "a reduction in the quantity of propoxyphene probably would not be accompanied by a reduction in abuse;. . .there is no relationship between the volume of distribution and the incidence of abuse."[7] But experience has proven that the more available a drug is, the more danger it will do. In a recent report called "Drug Scheduling--What Effects?," the authors state that "trends in abuse as measured by DAWN (Drug Abuse Warning Network),[8] roughly parallel trends in the extent of prescription use for those drugs, as measured by the NPA (National Prescription Audit)."[9] This positive correlation between prescriptions and abuse is aptly illustrated by the situations with amphetamines, methaqualone and barbiturates (excluding phenobarbital). Placement of these drugs in Schedule II, thereby disallowing refills, resulted in a 50% decrease in drug abuse incidents. Table 1[10] illuminates the superior effectiveness of Schedule II compared with Schedule IV in terms of reducing the number of prescriptions:

TABLE 1

EFFECT ON THE NUMBER OF PRESCRIPTIONS
OF PLACING DRUGS IN SCHEDULE IV OR SCHEDULE II

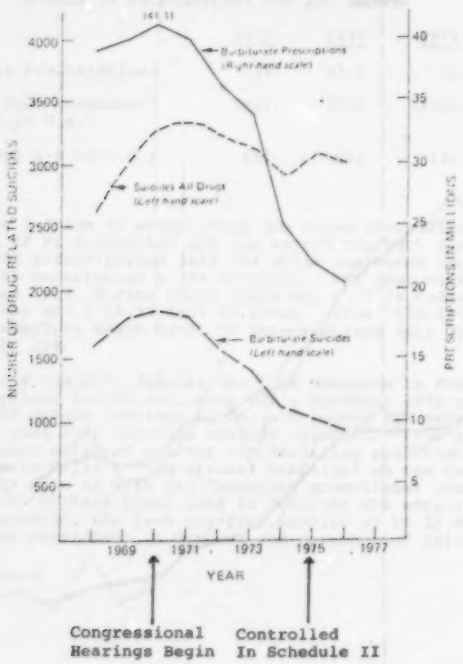
		Annual Number of Prescriptions (Millions)		
	Drug	Before Scheduling	1 Year After	% Change In Prescriptions
Schedule IV	Diazepam (Valium)	58 Million	54 Million	-6.9%
	Flurazepam (Dalmane)	11.5 Million	12.75 Million	+10.9%
	Propoxyphene (Darvon)	37 Million	33.5 Million	-9.5%
Schedule II	Amphetamines	16 Million	8 Million	-50.0%
	Methaqualone (Quaaludes)	42 Million	20 Million	-52.4%
	Seccobarbital (Seconal	8 Million	4.3 Million	-47.6%

Data from D.L. Crosby, et al., "Drug Scheduling--What Effects? (reference 10)

Figure 1[11] shows that restricting the availability of barbiturates by imposing Schedule II controls had a marked positive effect on reducing the number of barbiturate suicides, as well as decreasing the magnitude of all drug suicides. A Lilly representative recently stated that transferring PX to Schedule II would have "negligible impact on suicides" since abusers would merely "move to another drug."[12] However, Figure 1 suggests that people intending to commit suicide with barbiturates did not, for the most part, turn to other drugs for suicide. The graph shows that total drug suicides, as well as barbiturate suicides, have decreased.

Figure 1

SUICIDE INCIDENTS AND PRESCRIPTION TRENDS FOR BARBITURATES



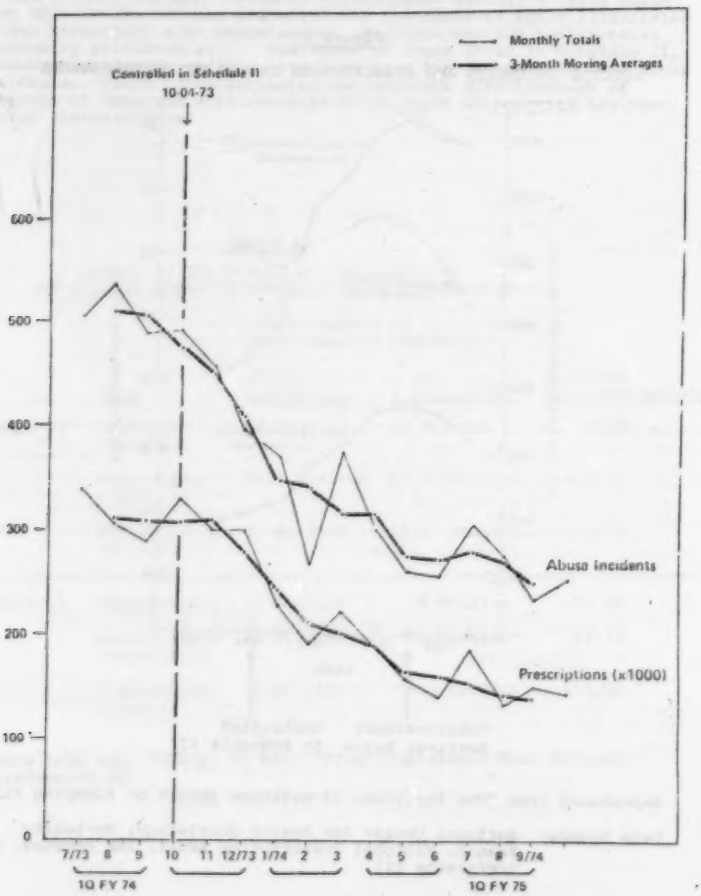
Reproduced from "The Institute of Medicine Report on Sleeping Pills."

Data Source: National Center for Health Statistics, Mortality Branch, National Prescription Audit, IMS America, Ltd. (reference 11)

Figure 2[13] illustrates that the imposition of Schedule II restrictions on methaqualone resulted in a marked decrease in all kinds of abuse incidents involving this drug. The close correlation between prescriptions and abuse incidents is striking.

Figure 2

ABUSE INCIDENTS AND PRESCRIPTION TRENDS FOR METHAQUALONE



Reproduced from the DEA report "Evaluating Drug Control Effectiveness" (reference 13)

Based on the experience of other Schedule II drugs, placing PX products in Schedule II will further contribute to the downward trend in prescription sales and abuse incidents that has already been witnessed as a result of the placement of PX in Schedule IV and the publicity surrounding the HRG petition and Congressional hearings.

In Table 2, the analogous downward trends for prescription sales and abuse incidents for PX during the past four years are evident:

TABLE 2

TRENDS IN PROPOXYPHENE USE AND ABUSE

	1976	1977	1978	1979
Millions of Prescriptions[14]	37	33.5	31	24.9
Emergency Room Mentions[15] (for 1/3 of U.S.)	3941	3758	3352	2817
Deaths[16] (for 1/3 of U.S.)	497	571	440	Data Incomplete

Figure 3 (page 6) exemplifies the close correlation between the amount of PX prescribed and the amount abused. Between 1976 and 1979, PX prescriptions fell 33% while emergency room abuse mentions for PX experienced a 29% decrease. The year with the largest decrease was 1979, during which there was a 19.7% reduction in prescriptions and a 16.2% fall in abuse. From 1976-1978, the last year with complete death data, PX prescriptions fell 16% and deaths decreased by 12%.

Figure 4 (page 7) depicts the time sequence in the decrease in prescriptions for PX following HRG's November 1978 petition, the January 1979 Senate hearings on PX, and former HEW Secretary Califano's June 1979 warnings against using PX.[17] The graph shows that the least affected quarter for declining prescription sales corresponds to Lilly's "educational campaign" on the dangers of Darvon. This fits in with the "standard promotional campaign" character which Dr. Richard Crout used to describe the activities of the Lilly salespeople, who gave out free samples of PX in more than 75% of visits to physicians in October and November of 1979.[18]

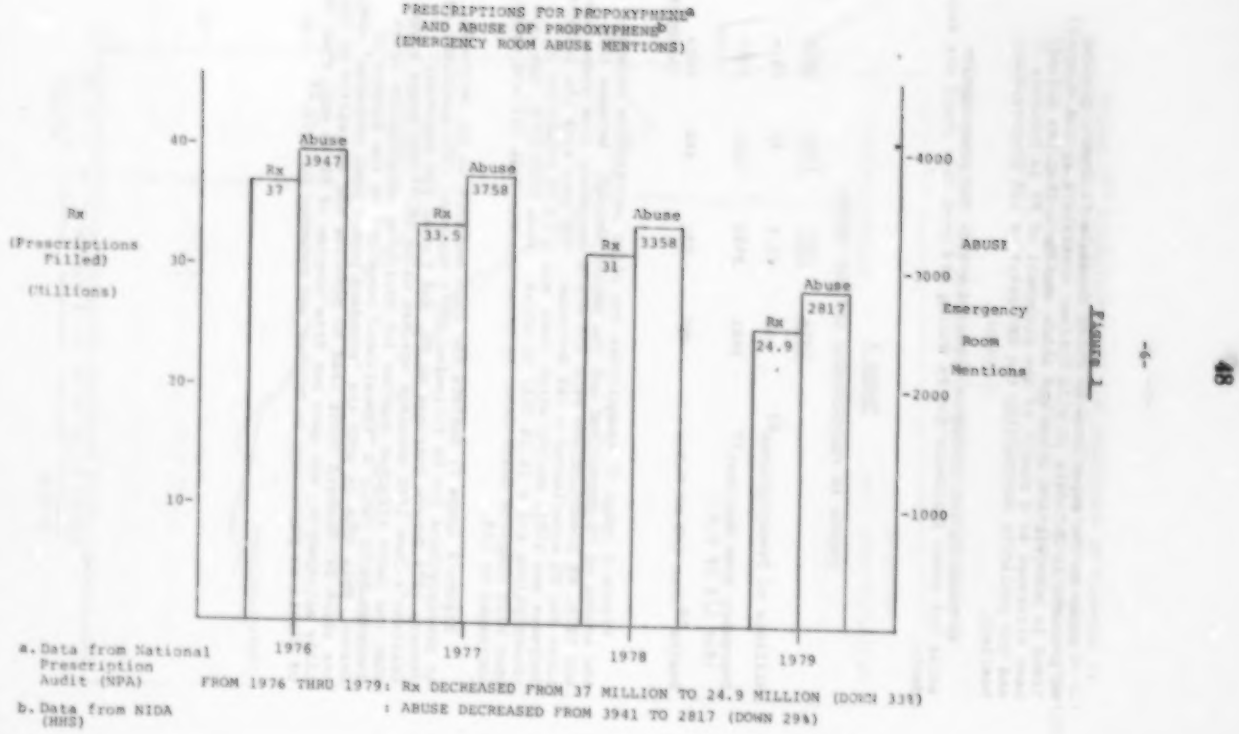


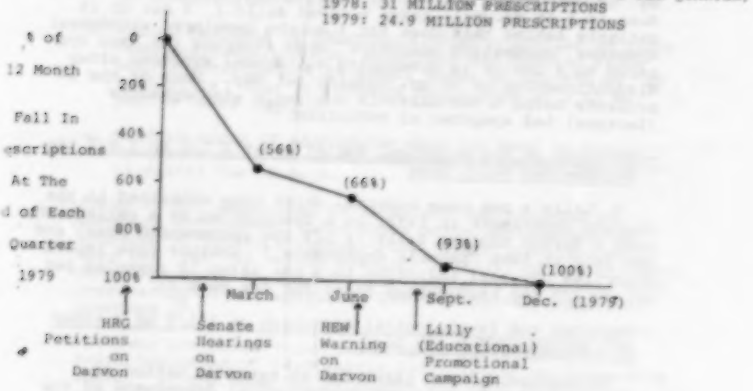
Figure 1

a. Data from National Prescription Audit (NPA)

b. Data from NIDA (HHS)

FROM 1976 THRU 1979: Rx DECREASED FROM 37 MILLION TO 24.9 MILLION (DOWN 33%)
: ABUSE DECREASED FROM 3941 TO 2817 (DOWN 29%)

Figure 4



Overall, general concern about the safety and efficacy of PX products has already contributed to a reduction in PX prescriptions and abuse incidents. Lilly's flimsy attempts at an educational campaign have taught us that we can't rely on them to disseminate vital information to physicians. FDA drug researchers Crosby et al. reported: "For drugs that were already experiencing a decline in use before scheduling requirements were initiated, a greater rate of decrease seemed to begin in the year of added control."[19] Thus, the only way to accelerate the decrease in PX prescriptions and abuse incidents is via an immediate transfer of all PX-containing products to Schedule II.

B. Addiction Liability

Evidence of dependence on PX is well documented in the literature. Clinical trials and published case histories illustrate that PX can produce physical addiction, as manifested by withdrawal symptoms, strong psychological dependence, and tolerance. Reports on PX dependence suggest addiction at less than the recommended daily dose of 390 mg. and unequivocally confirm addiction at twice the recommended daily dose.

1. Physical Addiction at 2/3 To Twice the Recommended Daily Dose

--Physical Addiction at 2/3 the Recommended Daily Dose

In a well controlled, double-blind study performed at Harvard Medical School, patients with pain were given 65 mg. of Darvon 4 times daily. (The maximum recommended daily dose is 1 65 mg. pill taken 6 times daily.) 3 out of 19 patients taking this dose for 3 months developed withdrawal symptoms "suggesting addiction" upon stopping the drug compared to 4 out of 16 developing withdrawal symptoms after discontinuation of 32 mg. codeine per day. None of the 14 patients using a non-narcotic analgesic ethoheptazine (Zactane) had symptoms of addiction.[20]

--Physical or Psychological Addiction at 1 1/3 to 1 2/3 the Recommended Daily Dose

In Lilly's own case reports, which they submitted to the Justice Department in 1970, is a description of a patient who took 8 Darvon tablets daily (1 1/3 the recommended dose) and was said to have "psychic dependence." Another case report describes physical addiction in a man using 10 capsules per day (1 2/3 the recommended dose) for one year.[21]

--Physical and Psychological Addiction at 1 1/3 to 2 times the Recommended Daily Dose

"Propoxyphene, when taken for an extended period of time, produces physical and psychological dependence of the morphine type. This may occur with as little as 500-800 mg. per day of the PX hydrochloride or 800-1200 mg. per day of the napsylate salt of PX (8-12 tablets/capsules per day)."[22]

(8-12 pills are 1 1/3 to 2 times the recommended daily dose.)

--Physical Addiction at 2 Times the Recommended Daily Dose

Jasinski et al. reported that "propoxyphene napsylate was identified predominantly as an opiate ('dope') by both subjects and observers, with a pattern of signs and symptoms similar to those produced by propoxyphene hydrochloride and morphine sulfate . . .propoxyphene napsylate clearly substituted for morphine and depressed abstinence." When a placebo was substituted after 3 weeks of treatment, "a mild opiate abstinence syndrome resulted," indicating that physical addiction to propoxyphene napsylate can occur at doses as low as twice the recommended daily dose.[23]

2. Additional Reports of PX Dependence

--Fraser and Isbell[24] provided evidence that PX has addiction liability by demonstrating that the drug can:

a. partially suppress the symptoms of morphine abstinence after 800 mg. (twice the recommended daily dose) is administered within one 24 hour period.

b. induce patients to experience effects similar to those from marijuana, heroin, morphine, and cocaine after oral administration in single doses of 355-650 mg. or 6-10 pills. (The recommended daily dose is 1 65 mg. pill 6 times daily.)

c. produce signs of abstinence when the drug is abruptly discontinued after administration of 600-825 mg. (10-13 pills) for 53 days.

--Inaba et al. found that PX napsylate administered in doses of 300-700 mg. given twice daily ameliorates the symptoms of opiate withdrawal and "significantly diminishes the 'yen' of heroin craving." 28%(9) of the patients noted "pleasant euphoria" after taking PX napsylate. With termination of PX napsylate, 19%(6) reported withdrawal symptoms.[25]

--Maletsky presented 7 new cases of PX addiction with no prior histories of psychiatric difficulties or other drug abuse. In one example, methadone was used to withdraw the patient from PX without difficulty. Maletsky concluded that the case reports demonstrate the following points relative to PX addiction:

"1. Addiction to PX can occur in individuals neither psychiatrically ill nor 'addiction prone.'

2. Addiction can occur under the usual circumstances of medical prescribing.

3. Tolerance and withdrawal can be clearly demonstrated.

4. Addiction can occur without initial euphoria."[26]

---Tennant reported that 30-40% of the 18 patients in a heroin and methadone detoxification program experienced an unpleasant "high" or hallucinations from PX napsylate, and 88% (16) experienced withdrawal sickness upon missing one daily dose of the drug.[27]

--In a study of 28 methadone maintenance patients undergoing detoxification with PX napsylate, 8 patients (28.6%) became physically addicted to the latter and experienced withdrawal symptoms when all drugs were discontinued.[28]

--In a recent letter to the editor of The Lancet, the author described a case of PX addiction and concluded: "The case described has all the hallmarks associated with addiction with opiates: prescription for the relief of chronic pain leading to tolerance and increasing dosage followed by dramatic withdrawal symptoms, only overcome by taking the drug once more."[29]

--Neonatal withdrawal symptoms have been reported in infants whose mothers had been chronic users of PX-containing products during gestation at the recommended or less than the recommended therapeutic dose.[30-32]

In light of the foregoing evidence of addiction potential and tolerance, it is inconceivable that Lilly reached the following conclusions:

> "Well-qualified experts have conducted repeated studies and evaluations of propoxyphene products since 1956 and have consistently found little evidence of dependence liability.[33] Published reports show only isolated and infrequent instances of dependence.[34] With respect to propoxyphene napsylate, Lilly is not aware of any published reports of dependence."[35]

According to Melmon and Morrelli, "the most prominent effects (of PX) may be its addictive quality."[36] The clear-cut evidence of addiction at just twice the recommended therapeutic dose notwithstanding, PX products are still classed in Schedule IV, despite the fact that certain drugs in Schedule II don't produce any greater degree of physical or psychic dependence than PX. For example, amphetamines, with less evidence of physical dependence than PX, are in Schedule II. Meyers et al. reported that "physical dependence (from amphetamines) manifested as withdrawal signs is difficult to establish."[37] In addition, PX is far more widely abused than amphetamines,[38] and when abused, it produces a comparable degree of psychological dependence and a greater degree of physical dependence. Thus, PX products represent an even stronger case than amphetamines for inclusion in Schedule II.

C. Weak Analgesic Properties

The relative ineffectiveness of PX as a painkiller lures unsuspecting patients to exceed the recommended daily dose. Documented evidence in the literature attests to the inferior analgesic efficacy of PX products:

--In a comprehensive survey of the published literature up to 1970, Miller et al. examined 243 articles on PX and found few hard data on its therapeutic value compared with other analgesics. 7 of the 16 reviewed studies comparing PX with placebo--4 of which used the manufacturer's suggested dose of 65 mg.--showed that PX was not superior to placebo. The authors concluded that "propoxyphene is no more effective than aspirin or codeine, and may even be inferior to these analgesics."[39]

--Hopkinson et al. compared the analgesic effect of 650 mg. acetaminophen plus 65 mg. of PX and acetaminophen plus a placebo. They found that PX was statistically no better than placebo in the relief of pain.[40]

--Charles Moertel, a noted cancer specialist at the Mayo Clinic, reported that a combination of 100 mg. PX napsylate with 650 mg. aspirin was no different in analgesic effect than 650 mg. aspirin, and consistently ranked lower than the combination of 65 mg. codeine plus 650 mg. aspirin.[41] During last year's Senate hearings on PX, Moertel testified that "based on our results, we would have to conclude that if Darvon alone has any pain relieving effect, this is trivial and simply doesn't match up to common, inexpensive over-the-counter drugs. We must also conclude that the combination of Darvon with aspirin holds no advantage to aspirin alone, and if a patient requires a stronger analgesic, the physician should prescribe some other more effective drug regimen. . . . For the treatment of severe pain, the use of Darvon either alone or in combination is grossly inadequate treatment and is really inhumane to the patient."[42]

--In a second literature review, Miller examined 13 double-blind studies of PX's analgesic effectiveness. In 8 of these, PX failed to exhibit any advantage over other analgesics, and in 3, PX was no more effective than placebo. Miller found only 2 well designed experiments comparing the analgesic efficacy of combinations of PX with other analgesics (see Hopkinson and Moertel above). He concluded that the analgesic properties of PX combination products (PX plus acetaminophen or aspirin) can be attributed to the ingredient other than the PX.[43]

Since no well controlled study shows that PX is more effective in pain relief than alternative medications, it is clear from a therapeutic standpoint that little would be lost by restricting the availability of PX by placing it in Schedule II. Furthermore, because there is no evidence that Darvon compounds--approximately 90% of PX sales--are any more effective or any less abused[44] than plain Darvon, all PX-containing products should be placed in Schedule II.

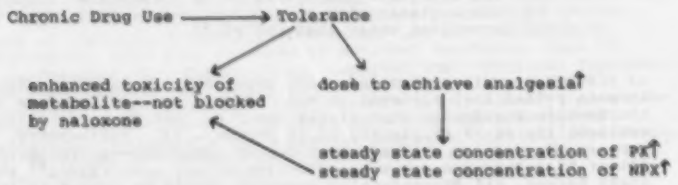
Moreover, since almost 90% of all prescriptions for PX are for combination products, 90% of those using the drug can tolerate aspirin or acetaminophen because they are already getting these drugs along with their PX. Thus, there is no identifiable target population for whom the drug offers any unique therapeutic benefit, no group of people who cannot tolerate aspirin, acetaminophen or codeine--all safer, cheaper and more effective than PX.

D. Toxicity

Considering PX's meager therapeutic efficacy at low doses and its euphoria-producing properties at higher doses, patients oftentimes increase their daily intake beyond the prescribed regimen in an attempt to achieve better pain relief or get high--and sometimes inadvertently become addicted. Taking into account the toxicity of PX-containing products, the potential to cause death in unsuspecting subjects is significant.(For a discussion on the large number of people having their prescriptions refilled at a rate that enables them to take more than the maximum recommended daily dosage of 6 pills per day, see p. 16)

Despite a claim by Eli Lilly and Company that "even when patients are administered large doses of propoxyphene over several weeks, neither the parent compound nor its metabolites accumulate in the blood," published data indicate the contrary.

When people use PX, the drug is metabolized by the liver to norpropoxyphene (NPX), an agent without any analgesic activity[45,46] or central nervous system toxic effects.[47,48] NPX, like PX, is cardiotoxic in high concentrations[49] and is suspected to contribute to the cardiotoxicity associated with PX overdoses.[50-52] The fact that NPX is cleared from the body more slowly than its parent compound[53] and reaches considerably higher blood levels than its precursor[54] suggests that the following sequence of events could occur in the chronic user of PX[55]:


Chronic Drug Use
Tolerance
enhanced toxicity of metabolite--not blocked by naloxone
dose to achieve analgesia↑
steady state concentration of PX↑
steady state concentration of NPX↑

According to Dr. Randall Baselt, FDA expert toxicology witness at the April 6, 1979 hearings on Darvon:

> "This accumulation of drug sets the stage for accidental overdosage: one or two additional depressant drugs, such as alcohol or diazepam, may be sufficient even in normally used amounts to cause death in susceptible persons."[56]

Table 3, constructed from published and unpublished data on blood levels of PX and NPX, illustrates the propensity of NPX to accumulate over time to amounts far in excess of PX. People chronically using PX at levels up to 6 pills per day (the recommended daily dose) can develop blood levels of PX of 0.24-0.85 micrograms per ml. and blood levels of NPX of 0.6-3.0 micrograms per ml. People using more than the recommended dose of PX-containing products without exceeding twice the recommended dose (7-12 pills) can develop blood levels of PX of 0.42-0.87 micrograms per ml., but NPX levels of 1.8-5.1 micrograms per ml. In the 6 subjects who were given 1 1/2 to 2 times the recommended daily dose, the average blood level of PX was 0.61 micrograms per ml. of blood, but the average level of NPX was 3.7 micrograms per ml.--more than 6 times higher than the PX level.

TABLE 3

BLOOD PROPOXYPHENE AND NORPROPOXYPHENE LEVELS IN REGULAR USERS OF PROPOXYPHENE PRODUCTS

Reference	Pills/day[a]	Type of Subject[b]	Duration of Drug Use	Maximum Blood Concentration[c] (µg/ml)	
				PX	NPX
57	3(HCL)	Cancer Patient	60 days	0.746(2)	3.01(2)
57	3(HCL)	Cancer Patient	14 days	0.275(2)	0.75(2)
57	3(HCL)	Normal Volunteer	4 days	0.241(2)	0.6 (4)
57	6(HCL)	Normal Volunteer	4 days	0.849(2)	1.24(6)
58	9(N)	Addict	28 days	0.519(3)	3.83(6)
58	11(N)	Addict	42 days	0.567(3)	4.94(9)
58	11(N)	Addict	84 days	0.513(6)	5.07(6)
58	12(N)	Addict	84 days	0.424(6)	1.83(6)
57	12(HCL)	Cancer Patient	365 days	0.866(2)	3.23(4)
59	12(N)	Addict	15 days	0.781(2)	3.26(2)

a The recommended daily dose is 1 pill every 4 hours or 6 pills per day.

HCL=propoxyphene hydrochloride N=propoxyphene napsylate

b The subjects include normal volunteers, cancer patients using propoxyphene products for pain relief and former addicts involved in addiction maintenance experiments.

c The number in parentheses represents the hours after the last dose when the maximum blood levels of propoxyphene and norpropoxyphene were attained.

Data from Verebelay and Inturrisi (1973), Inturissi (1979) and Gorodetsky (1979).

The fact that people using PX products at or slightly above the recommended dose can get NPX blood levels above 1 microgram per ml. is particularly alarming in view of the findings that:

1. In many cases of accidental death due to PX products, the blood NPX levels are in the same range as those found in chronic users of the drugs. In Table 4, 9 cases of accidental PX poisoning are listed, showing PX levels of 0.4-1.1 micrograms per ml. and NPX levels of 1.1-7.0 micrograms per ml. In 3 cases, no other drugs were being used, and in the remaining 6, alcohol was the only other substance detected. Blood alcohol levels in these 6 cases ranged from 0.04 grams% (one to two drinks) to 0.2 grams%--a level high enough by itself to cause intoxication but not sufficient, alone, to cause death.

TABLE 4

PROPOXYPHENE FATALITIES ATTRIBUTED TO ACCIDENTS OR ABUSE

Reference	Blood Propoxyphene Concentration (µg./ml.)	Blood Norpropoxyphene Concentration (µg./ml.)	Blood Alcohol Concentration (g.%)
60	0.4	2.4	0.19
61	0.6	1.1	0.161
61	0.8	1.6	0.085
61	0.6	2.1	0.04
61	0.9	2.3	0.13
62	0.4	1.4	0
63	1.1	5.1	0
63	0.8	2.3	0.2
63	0.6	7.0	0

Data from Baselt, et al. (1975), Christensen (1977), Caplan, et al. (1977) and McBay (1976).

2. Comparable blood levels (above 1 microgram per ml.) of NPX in animals can cause significant blockage of conduction through the heart--a toxicity which can lead to arrhythmias and death.[64,65]

Reports of human cases of PX overdosage in which patients had abnormal electrocardiograms, showing an inhibition of electrical conduction through the heart, began appearing in the medical literature in the early 1960's.[66] Although many PX deaths were said to be of cardiac origin, the first animal study on the cardiac toxicity of PX and NPX was not initiated by Lilly until 1976.

Because of the cardiotoxic effect of PX and NPX, many PX-related deaths reported to DAWN as suicidal overdoses may have actually occurred unintentionally after chronic usage of the drug. (The underreporting of accidental/unexpected deaths notwithstanding, PX still leads all other prescription drugs in the number of reported unintentional deaths.[67]) And there may be a significant number of deaths unrecorded by DAWN that are truly accidental for which the cardiotoxic phenomenon is responsible. Jørn Simonsen, reporting on 30 cases of accidental death due to PX, cited 2 instances in which the cause of death was initially considered natural until subsequent toxicological examination revealed high blood levels of PX sufficient to account for death. "This raises the question of how many undiscovered cases of dextropropoxyphene poisoning are wrongly registered as due to natural death."[68]

According to Dr. Larry Lewman, Multnomah County (Oregon) Medical Examiner, in testimony before the Senate Select Committee on Small Business:

> "The relative concentrations of norpropoxyphene and propoxyphene in the tissues is of vital importance in distinguishing between suicidal and accidental manner of death."[69]

Drs. Baselt and Lewman assert that most PX deaths are not suicides but accidents, as determined by NPX blood levels as high or higher than the PX level, a condition suggesting chronic use of the drug rather than one massive suicidal dose.[70] Baselt reported that, during a one year period in San Francisco between 1973-1975, 59% of PX-related deaths were due to accidental drug abuse or accidental normal usage, compared with 31% attributed to suicide.[71] Lewman estimated that 67% of all medical examiner mentions in his state are accidental.[72]

Furthermore, Jasinski has commented that "the toxicity that limits the abuse potential of propoxyphene napsylate also limits its usefulness as a therapeutic agent in treating narcotic addiction."[73] Recent experiments with mice by Peterson et al. demonstrated that PX impairs the drug metabolizing capacity of the liver. The authors concluded that, considering the high doses of PX used in maintenance and detoxification programs and the fact that the liver tends to concentrate PX (thereby prolonging contact with microsomes and interfering with their ability to break down drugs):

> "(I)f these observations have any relevance to the human situation, the knowledge that some narcotic addicts, many with histories of polydrug abuse, are ingesting high doses of a slowly absorbed, long acting drug that could be an inhibitor of their drug metabolizing enzymes may be clinically useful."[74]

In another article by Peterson et al., the investigators stated:

> "It is conceivable that propoxyphene will inhibit MFO (microsomal mixed-function oxidase or drug metabolizing) activities in man, and that combinations of otherwise non-lethal concentrations of propoxyphene and other depressant drugs could result in clinically significant inhibition of drug metabolism which could culminate in mortalities."[75]

Thus, in addition to the preponderance of studies illustrating that toxic levels of the metabolite NPX can accumulate in chronic PX users is recent data indicating dangers when PX is administered acutely in narcotic detoxification programs. In light of this evidence, a question posed in a March 12, 1977 editorial in the British Medical Journal seems particularly apt: "With all these caveats, how good is the case for using the drug at all?"[76]

II. Propoxyphene Abuse Potential

Introduction

A representative from Eli Lilly and Company recently testified that "more than 99.5% of those patients who received propoxyphene prescriptions acquired quantities of the drug consistent with FDA-approved labeling--that is, within the product's labeled dosage regimen."[77] This may be true, but there is evidence of significant overacquisition of PX via refills.

An FDA-sponsored study[78,79] used Prescription Card Service data on 2 million individuals in the U.S. to analyze patients receiving PX between February and November, 1978. Projected to the total U.S. population, the following conclusions were reached:

--Of the 11.6 million national propoxyphene users, 426,000 (4%) are having their prescriptions refilled at a rate that enables them to consume more than 180 pills a month, or more than the maximum recommended dose of 6 per day.

--Of these 426,000, 72,420 or 17% are obtaining, via refills, prescriptions for PX sufficient to take over 360 pills a month, or more than twice the maximum recommended dose of 6 per day. Commenting on this subgroup, the authors stated:

> "If the propoxyphene was consumed according to the prescription refill records, their daily consumption could have averaged 12 or more dosage units. Considering that dependence may occur if patients take as few as 8-12 dosage units per day, the implications are obvious."[80]

In view of the easy availability of PX, with Schedule IV allowing up to 5 refills within 6 months of the original prescription without contacting the physician, and the addiction at 1 1/2-2 times the recommended dose, the number of potential misusers of PX is quite large. Lilly has stated that "abuse is isolated, sporadic and insubstantial"[81] and "propoxyphene is not often abused for its psychic effects."[82] The following are examples of drug abuse studies which indicate that the intentional, non-therapeutic use of PX by a wide cross section of people is becoming a problem of epidemic dimension:

A. Adolescent Propoxyphene Abuse

--Although only 7% of all PX prescriptions are written for persons ages 10-19,[83] approximately 25% of the emergency room mentions for PX in 1978 involved people in this age group.[84] Of the top-ranking drugs in DAWN emergency rooms, PX ranked 7th among the adolescent subgroup.[85] Ranking above PX were alcohol-in-combination, aspirin, and acetaminophen--not surprising due to the easy availability of these substances. It is surprising, however, to see such a high magnitude of emergencies associated with PX, considering the unlikelihood of people in this age range having the drug prescribed for them. One possible explanation is that adolescents are obtaining PX from their family medicine cabinets.

--Drug use patterns were analyzed from a group of 365 adolescents referred by the courts because of alcohol problems in King County, Seattle, Washington. 10% of the sample population had used PX illicitly.[86]

--Between September 1976 and March 1977, the National Youth Polydrug Study surveyed 2,750 teenagers, 18 or younger. 488 subjects (17.7%) indicated that they had used Darvon or Darvon-N in their lifetimes, making PX the most frequently mentioned opiate drug. When ranked in terms of prevalence of "regular use" (i.e. at least once a week), Darvon/Darvon-N was second only to heroin.[87]

--Chambers and Taylor, in a National Institute of Mental Health (NIMH) funded study, examined illicit diversion of PX from legitimate medical channels and delineated, from their reservoir of experience with narcotic addicts, 6 patterns of PX abuse. Diffusion of PX among teenagers within a black Philadelphia ghetto exemplified PX's use as a primary drug of abuse. Ready availability and euphoria-producing effects were the two motivations which contributed to this choice.[88] Adolescents were also cited as representative of people using PX as a drug of chance experimentation. Data collected at a private suburban high school revealed that, of 112 female residents, 10% had abused PX at least 3 times.[89]

B. Propoxyphene Abuse In Other Age Groups

--A HEW-funded study of a stratified probability sample (by region, race, income, etc.) of 3,024 19-30 year old men, whose names were obtained from selective services records, found 14.9% had used PX for non-medical purposes. Projected to the total U.S. male population, this suggests that 3 million American men in this age range have used PX for non-therapeutic reasons.[90]

--In a DEA-sponsored study,[91] 14 drugs being used in a non-medical setting for non-medical purposes in 9 sites in the U.S. were studied for their contagious transmission. Contagious transmission is "the tendency of a psychoactive drug to spread spontaneously among related individuals in peer groups or association groups of some sort without any medical control."[92] Of 926 drug abusers undergoing treatment, 38% had used PX for its psychic effects. Those who reported using PX obtained the drug from friends, peers and dealers about 70% of the time and from medical sources approximately 20%. In about 40% of the sites studied, PX displayed contagious transmission by statistical definition. One of the authors concluded:

> "The importance of contagious transmission is that it is direct evidence of nonmedical use of a drug. If a drug is spreading by interpersonal contact among and within peer groups, its source has escaped from any medical controls (such as prescriptions). . . .The close correspondences between commonness of use, contagious spread, and illicit source of these drugs among treated users are suggestive of nonmedical use typically regarded as abusive."[93]

Chambers recently commented on the results of this study:

> "I believe Darvon dependence is a problem which still plagues us. However, I don't believe anyone is monitoring this type of dependence and that only a few isolated cases find their way into the literature."[94]

--Chambers and Taylor reported that, of 68 opiate addicts who said they had abused PX, 22.1% indicated their only or primary use of PX was as a substitute drug when the opiate of choice was in short supply. "One crude way to measure whether a drug has abuse potential is to determine whether it has a market value in the illicit subculture. By this measure, Darvon does have abuse potential."[95] Of 402 narcotic addicts queried, 37.6% said they had purchased PX from a pusher or knew of pushers who sold the drug.[96] Tennant reported: "Since today's heroin addict can seldom obtain from the illicit market more than 50-100 mg. per day of morphine equivalent, a dose of 800 mg. or less of propoxyphene napsylate would suppress effectively abstinence symptoms and provide adequate maintenance for many addicts."[97]

--Chambers and Taylor studied 6 addicts among whom PX was popular for counteracting the effects of injecting large doses of amphetamines and LSD. Despite the small sample size, the addicts' "statements and geographical distributions would tend to suggest the pattern is probably widespread."[98]

--Chambers and Taylor reported that in households which maintain a supply of propoxyphene for self-treatment without medical advice, self-treatment can move into the realm of abuse for psychic effect and dependence.[99] Smart and Fejer reported that, among those families where unnecessary analgesic and minor tranquilizer abuse exists, children carry a heightened probability of experimenting with potentially addicting drugs.[100]

--In a recent paper presented to the FDA Drug Abuse Advisory Committee,[101] Chambers reported data collected on all patients receiving emergency room care for drug-related incidents at the Jackson Memorial Hospital in Miami, Florida during January 1, 1972 - December 31, 1975. During the 4 year period, 2%(148) of the 7,143 cases in which a drug was the primary substance involved propoxyphene. On the average:

--the vast majority of PX mentions were for women(68%)

--more than 1/2 the PX cases were blacks (51%)

--more than 3/4 the PX mentions were for patients under 35

--29% of the PX-related incidents were suicide attempts, with the remaining 71% reflecting "accidental overdoses, allergic reactions, psychotic reactions or withdrawal symptoms."

--44%(65) of the mentions for PX involved another drug, with more than 67% of these being some other central nervous system depressant.

--Several methadone clinics have reported significant use of PX by addicts. In 1978 in New Orleans, of 171 urine samples which showed evidence of drugs, 104(61%) were positive for PX, making PX the most frequent drug detected. Methadone treatment programs in New Mexico and California reported that about 25% of all urine samples showed PX.[102]

--Tennant reported in detail the non-therapeutic use of PX hydrochloride which occurred among American soldiers stationed in West Germany during 1969-1971. A survey indicated that "approximately 15-20% of the 180,000 American soldiers in West Germany had used propoxyphene one or more times for non-medical reasons."[103]

--Regarding the reasons for using PX, only 21% of the emergency room patients in 1978 mentioned their motivation as psychic effect or dependence.[104] Farley and Santo stated that "crisis center clients reporting use of this drug appear to be quite different in this regard: over half of them(51%) indicated they took the drug for its psychic effects."[105]

C. Propoxyphene In Combination With Other Substances

Certain drugs, such as alcohol and tranquilizers, enhance the activity of PX by having a synergistic depressant effect on the central nervous system. There is recent evidence that other drugs can potentiate the effect of PX by reducing the metabolism of PX by the liver.[106] Mixing PX with alcohol or other central nervous system depressants can cut down considerably the amount of drug which constitutes a lethal dose.

The following chart, derived from DAWN data,[107] illustrates the propensity for misuse of PX in combination with other substances:

TABLE 5

PERCENTAGE OF MENTIONS OF PROPOXYPHENE IN COMBINATION WITH ANOTHER DRUG/SUBSTANCE

	1976	1977	1978	1979
Emergency Rooms	64%	63%	64%	66%
Medical Examiners	74%	62%	79%	Data Incomplete

--For the years 1976-1979, a total of 322 different combination names were reported in DAWN involving PX. 168 (52%) involved PX plus an illegal substance.[108]

--In a recent letter to the editor of the Canadian Medical Association Journal, Dr. Rosser, Director of the faculty of medicine at the University of Ottawa in Ontario, reported:

> "(S)ince 1972 there has been a steady increase in the number of deaths resulting from misuse of the analgesic drug propoxyphene. Many of the deaths occurred when patients combined propoxyphene with alcohol, other central nervous system depressant drugs or a combination."[109]

--In a recent article on Distalgesic (Darvocet-N) use in the United Kingdom, the authors reported that: "Distalgesic accounts for most overdoses" and that "it has become an increasingly popular component of self-poisoning cocktails." They concluded that "the rise in incidence of Distalgesic poisonings has followed remarkably closely the recent rise in the prescription rate for analgesics containing dextropropoxyphene" and suggested "restrictions on the availability of the drug" as a means to curb abuse.[110]

In a February 5, 1980 FDA memo reviewing the IMS National Detailing Audit survey of Lilly's educational campaign--which Lilly interpreted as showing that "physicians have a very high awareness level of precautions applicable to the prescribing of Darvon products"[111]--FDA Prescription Drug Labeling Staff Psychologist Dr. Louis Morris commented on Lilly's failure to impart information on PX's risks:

> "(O)nly 20 physicians of the 300 surveyed (7%) spontaneously recalled having been informed about the dangers of using Darvon with alcohol. Other precautions, such as use with other depressants or with emotionally disturbed patients, were recalled to an even lesser extent.. . .Although the probed recall questions show a high rate of physicians agreeing that caution is needed when prescribing Darvon, the unaided recall questions suggest that this information is not part of the physicians' active repertoire of information utilized when making prescribing decisions."[112]

D. New Evidence of Propoxyphene Use

The data generated by a recent pilot program illustrates that the intentional,non-therapeutic use of PX may be more widespread than commonly believed.

A National Institute on Drug Abuse (NIDA) sponsored study[113] of a random sampling of arrestees in 3 major cities during January and February of 1978 detected patterns of PX use not heretofore disclosed by information supplied by medical examiners and hospital emergency room staff(DAWN) and by federally supported drug treatment programs (CODAP). Using a jail-based urine screening approach, the results show a relatively high incidence of PX use among jail admissions. In Maricopa County in Phoenix, Arizona, PX was the most commonly used drug among arrestees, accounting for 30(39%) of the 77 drug mentions recorded during the data collection period. In Dade County in Miami, Florida and Erie County in Buffalo, New York, PX was second only to morphine/quinine as the most common drug detected. (See Table 6[114].)

TABLE 6

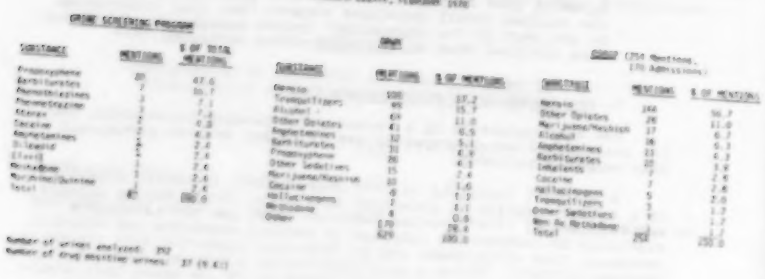
TOP RANKING DRUGS RECORDED BY THE URINE SCREENING PROGRAM
JANUARY-FEBRUARY 1978

	Phoenix		Miami		Buffalo	
	# Of Mentions	%	# Of Mentions	%	# Of Mentions	%
Propoxyphene	30	39	29	15	7	13
Morphine/Quinine	8	10	83	43	11	20
Methadone	7	9	16	8	4	7
Codeine	2	3	2	1	6	11
Barbiturates	13	17	13	8	7	13
Amphetamines	1	1	2	1	3	6
Cocaine	2	3	20	10	0	0
Other	14	18	28	15	16	30
	77	100	193	100	54	100

Data from F.M. Tims, "Monitoring Drug Use in the Community Through a Jail Urine Screening Program" (reference 114)

A comparison of the urinalysis findings in Maricopa County with data by DAWN and CODAP for February 1978 (Table 7[115]) illustrates that PX figured more prominently in the jail screening program than in either of the other systems. For example, in the urine screening program, 20 PX mentions accounted for 47.6% of the total mentions, whereas in the DAWN system, 26 PX mentions only represented 4.1% of the total.

TABLE 7



Reproduced from P.M. Tims, "Monitoring Drug Use in the Community Through a Jail Urine Screening Program." (reference 115)

Although some of the PX used by the arrestees was undoubtedly for legitimate medical purposes, much or most of it might be illicit. One limitation to this study is that, because the arrestees were not interviewed, no conclusions can be drawn regarding motivations for taking the drug. However, the results do illustrate the utility of a jail urine screening program for providing a perspective on drug use and trends not within the purview of existing studies. Information supplied by an ongoing jail urine screening program could be valuable in evaluating local drug use patterns and serve to complement the DAWN and CODAP systems in identifying emerging drug abuse problems.

That PX is extensively abused is evident from the above examples of drug studies. Abusers represent the gamut of socioeconomic strata and age groups, ranging from black ghetto adolescents to white, suburban adults. A wide spectrum of motivations cuts across this heterogeneous group of people; abusers include those without any previous drug abuse experience, those using PX for its euphoria-producing effects, as well as hard-core narcotic addicts.

Until all PX-containing products are placed in Schedule II and refills banned, we will continue to witness large numbers of unnecessary injuries and deaths predictably associated with the easy accessibility of these drugs.

III. A Comparison Of Propoxyphene and Codeine

Eli Lilly's contention that "the California experience suggests that reducing the availability of propoxyphene products will have little or no effect on their abuse but will increase codeine abuse"[116] is patently absurd for the following reasons[117]:

--There is no data on codeine abuse in California prior to the removal of PX from the Medicaid formulary (1970-1971) to which current codeine abuse can be compared to imply that PX restriction is causal.

--There is no data on PX abuse among Medicaid recipients before or after Medicaid restriction of PX to support the idea that abuse was not changed by restriction.

--Since Medicaid accounts for less than 10% of all prescriptions in California, and because the Lilly statistics on current codeine abuse are for the entire nation, even if codeine abuse in Medicaid recipients had increased, it would not likely show up nationally in all drug users.

NIDA's Action/Warning System records trends in DAWN emergency room mentions for selected drugs in 24 metropolitan areas. When mentions from the 4 quarters of 1979 are compared with the average mentions of the previous 6 quarters (July 1977-December 1978), the following results were obtained[118]:

--12 cities with no statistically significant change in any quarter in PX abuse (Boston, Buffalo, Kansas City, Miami, Minneapolis, New Orleans, Norfolk, Oklahoma City, Phoenix, San Diego, Seattle, and Washington, D.C.)

--11 cities with a statistically significant decrease in PX abuse (Atlanta, Chicago, Cleveland, Dallas, Denver, Detroit, Los Angeles, New York, Philadelphia, San Antonio, and San Francisco)

--1 city with a statistically significant increase in PX abuse (Indianapolis, home of Eli Lilly and Company)

For the 11 metropolitan areas where PX emergency room mentions decreased significantly (including the California cities Los Angeles and San Francisco), a significant increase in codeine abuse was recorded in only 2 (Detroit and Philadelphia). For the 12 metropolitan areas where no significant change in emergency room mentions for propoxyphene was recorded, a significant increase in codeine abuse was noted in only 3 (Buffalo, Miami and Washington, D.C.).

Overall, for the whole country, there was a statistically significant decrease in emergency room mentions for PX during the 2nd, 3rd and 4th quarters of 1979 with no statistically significant concomitant national change in codeine or oxycodone abuse. This last finding is of particular interest in view of Lilly's Quarterly Report to the FDA describing "increased demand for oral codeine preparations"[119] in conjunction with decreased utilization of PX.

Thus, decreased prescribing of PX and the attendant decrease in abuse has not been accompanied, either locally or nationally, by increased codeine abuse as implied by Lilly.

As far as intrinsic properties of PX and codeine are concerned, PX "is at least as toxic as codeine,"[120] yet PX is considerably less effective than codeine.[121,122] Moreover, in a recent article by Jasinski, the relative availability and relative incidence of abuse based on DAWN mentions were found to be 1.9 and 2.2 times higher, respectively, for PX than for codeine.[123] In recommending to the U.N. a transfer of PX to International Narcotics Schedule II, World Health Organization Director-General Mahler wrote that "dextropropoxyphene is liable to similar abuse and productive of similar ill effects as the drugs in Schedule II of these conventions (codeine and codeine analogs)."[124]

According to DAWN and National Prescription Audit data, the rates for both death and emergency room mentions for PX are considerably in excess of those for codeine-containing products.[125] Table 8 shows that in 1978, the last year with complete death data, medical examiner mentions were 42.6 per million PX prescriptions and 20 per million codeine and codeine combination product prescriptions.

TABLE 8

DEATHS FROM PROPOXYPHENE AND CODEINE-CONTAINING PRODUCTS

Drug	1978 DAWN Deaths[126] (1/3 of U.S.)	Estimated Total US Deaths For 1978	1978 Prescriptions[127] (in millions)	Total Deaths Per Million Prescriptions
Propoxyphene	440	1320	31	42.6
Codeine Products	298	894	44.8	20

Table 9 gives the emergency room mentions for PX and codeine products for 1979, indicating that emergency room mentions were 339.4 per million prescriptions for PX and 211.4 for codeine and codeine preparations.

TABLE 9

REPORTED NON-FATAL ABUSE OF PROPOXYPHENE AND CODEINE-CONTAINING PRODUCTS

rug	1979 DAWN Emergency Room Mentions[128] (1/3 of U.S.)	Estimated Total Emergency Room Mentions In U.S. For 1979	1979 Prescriptions[129] (In Millions)	Total Emergency Room Mentions Per Million Prescriptions
ropoxyphene	2817	8451	24.9	339.4
odeine Products	3284	9852	46.6	211.4

From these data, and from the testimony of Dr. Arthur McBay, Chief Toxicologist of North Carolina, that the number of codeine-related deaths is overstated,[130] it appears that PX is more dangerous and more widely abused than codeine products and should be more--not less--strictly controlled than codeine products.

IV. U.S. and International Support for More Stringent Controls On Propoxyphene

Voices within American medicine have spoken out against PX--from several directors of public hospitals who have banned the drug for being worthless, expensive, and dangerous, to coroners around the nation who do autopsies on victims of PX abuse. 13 out of 15 coroners responding to an HRG questionnaire 1 year ago who commented on regulatory action recommended banning PX-containing products or placing them in Schedule II. Coroners supporting these regulatory actions were from San Francisco, Philadelphia, Las Vegas, Oklahoma, North Carolina, Rhode Island, Los Angeles, Oregon (state), Portland (Oregon), Maine, Charlestown, Miami, and Milwaukee.

Outside of the U.S., the most detailed information on PX Abuse comes from Canada, where the Chief Coroners of all Canadian provinces recently initiated a national survey to monitor PX-associated deaths.

According to Dr. Stewart McMillan, Chief Medical Examiner of Saskatchewan, at a December 2, 1979 meeting of the Canadian National Association of Chief Coroners, it was unanimously agreed that PX should be placed under tight narcotic controls with no refills and no phone prescriptions. Several weeks ago, as a result of the U.N. decision to require all 110 signatories of the 1961 Drug Convention (including Canada) to impose production quotas on PX, the Canadian National Association of Chief Coroners wrote to Canadian Minister of Health Monique Begin requesting that she institute "no refill" and "no phone prescription" policies for PX products.[131]

Recent remarks from other world governments indicate that PX abuse is not limited to this continent.[132]

DENMARK: "Dextropropoxyphene is often encountered in cases of multi-drug abuse or in combination with alcohol or prescription medicine."

NETHERLANDS: "Dextropropoxyphene is occasionally found on a drug abuser."

NORWAY: "Only dextropropoxyphene has occasionally been found to be a component of pharmaceutical preparations sent for analysis."

PHILIPPINES: Abuse of dextropropoxyphene (combined with dipyrone) was found to be prevalent among former heroin users from low-income groups."

PORTUGAL: "Abuse of propoxyphene is growing. . .and should be placed under international control as soon as possible."

SWEDEN: "Legally obtained preparations containing dextropropoxyphene have, to a limited extent, been connected with abuse and suicide."

In addition, a recent study by the International Criminal Police Organization (INTERPOL)[133] on the appearance of certain psychoactive substances in illicit traffic reported that seizures of PX by police in 1977 and 1978 had occurred in the following INTERPOL countries:

Argentina, Belgium, Canada, Denmark, Hong Kong, Sweden, the United Kingdom, and the United States.

CONCLUSION

The Health Research Group recommends that all PX-containing products be immediately controlled under Schedule II as agents which demonstrate considerable addiction potential, abuse liability, human toxicity, and which have limited therapeutic usefulness. We believe that the minimum controls of Schedule IV are not sufficient to protect the public from the dangers of PX. As long as PX-containing products remain in Schedule IV, this regime will continue to have a lesser impact on the amount of abuse than could be attained with stringent Schedule II controls.

Schedule III, which also allows up to 5 refills within 6 months of the original prescription without contacting the physician, would be an unacceptable alternative to Schedule II. Prior to their switch to Schedule II, both amphetamines and barbiturates spent a brief tenure in Schedule III. More stringent controls were imposed after Schedule III failed to have a major impact on prescription sales and abuse of these drugs. It seems highly probable that a parallel situation would ensue if PX products were switched to Schedule III.

In a September 28, 1979 addendum to a position paper submitted the previous day to the Propoxyphene Task Force, NIMH drug researcher Dr. Candace Pert commented:

> "The best thing the Task Force could accomplish would be to urge the immediate rescheduling of propoxyphene from Schedule IV to Schedule II. . . .(T)he relevant issues have been hashed and rehashed and the arguments for rescheduling propoxyphene remain convincing. . . . Frankly, the foot-dragging on rescheduling this worthless, dangerous and scientifically well understood drug suggests that extremely serious problems in our drug regulation procedures exist."[134]

That this drug, associated with roughly 11,000 deaths and 79,000 emergency room visits for the whole country since September 1972,[135] is a serious health problem is not disputable. Only by an extreme decrease in prescriptions via Schedule II controls will this public health problem be significantly reduced. It will take more than Lilly's "educational campaign" to undo the harm caused by 23 years of slick, oftentimes erroneous, but obviously successful advertising of PX products by Lilly.

The undersigned certify that, to the best of their knowledge and belief, this petition includes all data, information, and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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FOOTNOTES

1. Controlled Substances Act, 21 U.S.C. §§ 811, 812(b)(2).

2. HEW Quarterly Report on Propoxyphene, Third Quarter 1978-Fourth Quarter 1979, p. 2.

3. DEA, "Compliance Survey Regarding Propoxyphene," to the FDA, U.S. Department of Justice, Washington, D.C., March 20, 1979, p. 5.

4. Morris, L., memorandum on the Lilly Quarterly Report on Darvon, to the Director of the Division of Drug Experience, February 5, 1980.

5. Maletsky, B.M., "Addiction to Propoxyphene (Darvon): A Second Look," Int. J. Addict.,9(6): 775-784, 1974, p. 781.

6. DEA report, op. cit., p. 5.

7. Eli Lilly and Company, "Submission Regarding Propoxyphene to the FDA Drug Abuse Advisory Committee," April 17, 1979, p. 41.

8. The DAWN system is based on information supplied by medical examiners and hospital emergency room staff in selected metropolitan areas. DAWN statistics represent drug abuse data from approximately 1/3 of the country.

9. Crosby, D.L., et al., "Drug Scheduling-What Effects?," Drug Use Analysis Branch of the FDA, presented at the American Pharmaceutical Association Annual Meeting, Montreal, May 1978, p. 7.

10. Ibid., graphs 1-6.

11. Reproduced from the "Institute of Medicine Report on Sleeping Pills," April 1979.

12. Furman, R.H., in response to a question by Congressman Leland during Congressional hearings on Darvon, May 21, 1980.

13. Reproduced from DEA report "Evaluating Drug Control Effectiveness," U.S. Department of Justice, Washington D.C., June 1975, p. 16.

14. Data from National Prescription Audit, Therapeutic Category Report, IMS America, 1978 and 1979 editions.

15. DEA computer run, March 31, 1980, tape of consistently reporting medical examiners and emergency rooms.

16. Ibid.

17. In a June 15, 1979 statement, then Secretary of HEW Joseph Califano cautioned: "Never use Darvon and other propoxyphene products unless there is really no alternative, and then only with care."

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38. DAWN Annual Report, IMS America, 1978, pp. 63 and 66. Accounting for all mentions in the total DAWN system, there were 2736 emergency room mentions and 53 medical examiner mentions for amphetamines in 1978. The numbers of emergency room and medical examiner mentions for PX were 3938 and 454 respectively--considerably higher than those for amphetamines.

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42. Moertel, C.G., testimony before the Select Committee on Small Business, U.S. Senate, in Competitive Problems in the Drug Industry, Part 34, U.S. Government, Washington, D.C., 1979, pp. 16641 and 16642.

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44. In a recent National Institute on Drug Abuse (NIDA) report entitled "An Analysis of d-Propoxyphene Mentions Reported to the Drug Abuse Warning Network, 1978," Table 2 gives the trade names of PX products reported to DAWN during the first 10 months of 1978. 97.5% of the mentions were for Lilly PX products. Of these, 56.6% were for plain Darvon and 40.9% were for Darvon combination products. According to the authors of the study, in light of the fact that about 90% of PX sales are for combination products, it is highly likely that the familiar name Darvon is being cited carelessly when, in effect, combination products were abused. Because the plain Darvon category probably represents a hodgepodge of all PX-containing products, the number of mentions for Darvon combination products is clearly an understatement of those instances in which combinations are involved.

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58. Inturrisi, C.E., personal communciation to Dr. Sidney M. Wolfe, January 29, 1979.

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125. Despite the fact that plain codeine is in Schedule II and codeine combination products are in Schedules III and V of the Controlled Substances Act, a statistical comparison of PX products to all codeine-containing products is a valid one since there is no good evidence that codeine preparations are less abused than plain codeine. In 1978, for example, there were reported to be 287 medical examiner mentions for Schedule II codeine but only 11 medical examiner mentions for codeine combinations--highly unlikely, according to Chief of DEA's Regulatory Control Division Howard McClain, considering that "85-90% of the codeine consumed is Schedule III and V preparations." (Personal communication to Pauline Sobel, May 29, 1980.) Emergency room mentions for the years 1976-1979 for codeine combinations were only 2-3 times higher than similar mentions for plain codeine, despite the fact that 9 times more codeine is sold in combination form--indicating an overreporting of Schedule II codeine emergency room mentions and an underreporting of those for codeine combinations.

Several people with whom we have spoken to recently concurred that the DAWN codeine statistics are fraught with ambiguity. According to Nick Kozel, Chief of NIDA's Forecasting Branch, "there is definitely error in terms of calling a combination drug plain codeine since codeine is such a common name. Hospital emergency room reports are based on patients' reporting rather than toxicology reports, which distorts the statistics." (Personal communication to Pauline Sobel, May 27 and 29, 1980.) Carol Anglin, Vice President of Macro Systems, Inc. and co-author of a soon-to-be-published validity study on drug reporting, asserts that "thorough toxicology is not always performed by medical examiners, so codeine combination products are frequently reported as plain codeine." (Personal communication to Pauline Sobel, May 29, 1980.) Charlie Chu of the Regulatory Control Division of the DEA stated that "all codeine medical examiner mentions are basically for combination products. I would be very skeptical about plain codeine mentions." (Personal communication to Pauline Sobel, May 29, 1980.)

Thus, a comparison of PX products to all codeine-containing products is justifiable on the basis that, because of the inaccuracy of DAWN codeine statistics, the relative frequency of the abuse of codeine and codeine preparations cannot be adequately assessed.

126. DEA computer runs, March 31, 1980 tape.

127. Data from National Prescription Audit, op. cit., 1979.

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129. Data from National Prescription Audit, op. cit., 1979.

130. McBay, A.J., Statement Before the Monopoly and Anticompetitive Activities Subcommittee of the Select Committee on Small Business, January 31, 1979.

131. McMillan, S., personal communication to Dr. Sidney M. Wolfe, May 1980.

132. Replies received by August 31, 1979 from world governments in response to a request for information on 5 drugs (including PX) by U.N. Secretary-General Waldheim.

133. INTERPOL, "Review of Psychoactive Substances for International Control," July 27, 1979.

134. Pert, C.B., "Addendum to Position Paper Submitted September 19, 1979," to Dr. Ronald Kartzinel, Chairman of the Propoxyphene Task Force, September 20, 1979.

135. DAWN data, September 1972-December 1979.

Mr. WAXMAN. Our next witness is Jere E. Goyan, Commissioner of the Food and Drug Administration. Dr. Goyan is representing the new Department of Health and Human Services and will review for us the Department's current activities regarding propoxyphene. Dr. Goyan, I know you have a lengthy statement which, without objection, we will insert in the record in its entirety. [See p. 83.] What I would like you to do, if you would, would be to summarize your statement so we will have an opportunity for questions.

STATEMENT OF JERE E. GOYAN, PH. D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF FOODS; AND NANCY L. BUC, GENERAL COUNSEL

Dr. GOYAN. Thank you, Mr. Chairman.

I am accompanied by Nancy Buc, General Counsel of the Food and Drug Administration, and Dr. Crout, Director of the Bureau of Foods, Food and Drug Administration.

Before starting my testimony in this regard, Mr. Chairman, I would like to extend my congratulations to you and the members of the committee on your rapid handling of the infant formula problem that we shared some time ago. I was very pleased that the bill passed the House yesterday. Thank you very much.

I am pleased, of course, to represent the Department of Health and Human Services here today to bring you up to date on our activities with respect to the drug propoxyphene. I think we can skip over most of the background but I think it is important to note that the combination products are clearly effective even though the contribution of their propoxyphene component may be relatively small. Propoxyphene has been marketed in an array of dosage forms, combinations, and salts that offer physicians a wide variety of options for managing patients with painful disorders. Many physicians believe that no other prescription analgesic possesses a combination of properties so attractive to the general physician for the management of patients with mild to moderate pain. It does not carry the risks of serious gastrointestinal bleeding

associated with aspirin, the liver damage associated with overdoses of acetaminophen, or the kidney damage associated with phenacetin. Neither does propoxyphene cause drowsiness or constipation to the same extent as codeine.

Propoxyphene is structurally related to the narcotic analgesic methadone. Although its general pharmacological properties are those of the narcotics as a group, the potency of propoxyphene hydrochloride is from one-half to two-thirds that of codeine. Compared with other prescription analgesics, the adverse reactions associated with propoxyphene are mild and infrequent when the drug is taken as directed. It is terribly important to remember when taken as directed it does not have those problems.

However, the abuse potential of propoxyphene was recognized as early as the late 1950's but was not a major public health concern until the late 1960's and early 1970's. Chronic use of high doses of propoxyphene can produce physical and psychological dependence that has characteristics similar to that associated with morphine-like drugs but is much lower in intensity and relatively much less common. Intravenous "street" use by drug abusers was once popular in the late 1960's, but this practice waned, partly because propoxyphene damages blood vessels and injures tissue at the injection site.

The epidemiologic data on propoxyphene fatalities have consistently shown that the majority of deaths occurred because of deliberate overuse, abuse, and suicide. If the ratio of all deaths reported to DAWN relative to prescription use according to the national prescription audit is calculated, the propoxyphene group of drugs rank third behind short-acting barbiturates and sedative hypnotics as a cause of deaths, as summarized in appendix 2.

The FDA is not aware of any cases in which death was caused by propoxyphene products when taken alone in recommended doses and in which neither alcohol nor tranquilizers were also involved.

I would like to go on and talk now about the regulatory actions that have been taken. At the outset of my remarks I will say that in 1972, because of misleading statements on the effectiveness of Darvon made to physicians in a letter from Eli Lilly & Co., we required the manufacturer to issue a "Dear Doctor" letter stating:

> There is no substantial evidence to demonstrate that 65 mg of Darvon (DPX-HCl) is more effective than 650 mg of aspirin (two 5-grain tablets), and the preponderance of evidence indicates that it may be somewhat less effective.

In April 1976 FDA's Controlled Substances Advisory Committee (CSAC) recommended that propoxyphene—and its salts and preparations—be controlled in schedule IV of the CSA.

FDA and HEW concurred with the CSAC's recommendation, and DEA, therefore, in March 1977 placed propoxyphene, its salts and preparations, in schedule IV of the Controlled Substances Act.

Labeling for propoxyphene was further revised in 1978 to add a warning against the additive depressant effect of the products when used in conjunction with alcohol, tranquilizers, sedative hypnotics, and other central nervous system depressants and to require additional information on adverse reactions, drug interactions, and management of overdosage. A warning against use of the products during pregnancy was also added because of the danger of

propoxyphene causing physical dependence in the fetus, leading to neonatal withdrawal syndrome.

Those actions took place some time ago. As we are all aware, during the last year there have been a number of discussions of propoxyphene and the drug Darvon.

On November 22, 1978, the Secretary of the Department of Health, Education, and Welfare was asked by the Health Research Group (HRG) to suspend approval of the NDA's for propoxyphene-containing products and you know the subsequent actions on that.

The Secretary, however, in denying the HRG petition did direct the FDA to take the following actions:

Distribute an FDA drug bulletin to physicians and health professionals advising of the risks associated with the use of and abuse potential of propoxyphene. An article was published in the February-March 1979 issue of FDA Drug Bulletin in this regard. The drug bulletin is mailed to more than a million health professionals in the United States. Propoxyphene also was the subject of articles in the May-July 1977 and March-April 1978 Drug Bulletins; and

Disseminate information on the risks of propoxyphene to the public. An article, "Darvon subject to misuse," appeared in the March 1979 issue of FDA's official magazine, FDA Consumer, and more than half a million copies were reprinted and distributed through FDA's field offices—through the Consumer Information Center in Pueblo, Colo.,—and in supermarkets across the Nation. In addition, update articles on Darvon appeared in FDA Consumer magazine in the July-August, October, and November 1979 issues.

An earlier article that appeared in FDA Consumer in November 1976, entitled "Controls Urged on Top Rx Pain Drug," also had been reprinted and half a million copies distributed.

In March 1979, in conjunction with the article in FDA Consumer, FDA mailed to every radio station in the United States public service announcements on the dangers of propoxyphene abuse.

The Secretary also asked us to hold a hearing to allow the public an opportunity to present additional evidence on the benefits and risks of propoxyphene and that was held on April 6, 1979.

The Secretary asked us to complete by June 1979 the administrative process on the possible rescheduling of propoxyphene, including review by the Drug Abuse Advisory Committee. That meeting was held April 17, 1979.

On July 15, 1979, the Secretary announced his conclusion that DPX should remain in schedule IV but indicated simultaneously his concern that propoxyphene may better satisfy certain of the legal criteria for schedule II than for schedule IV of the CSA. He also asked the Assistant Secretary for Health to establish an interagency task force made up of representatives of FDA, NIH, and NIMH to summarize all pharmacologic data, epidemiology data, and outline new areas for needed research on the abuse potential of propoxyphene.

The FDA also took the following actions at that time:

Required all manufacturers of propoxyphene drug products to revise the physicians labeling to include the new warnings;

Issued a second FDA Drug Bulletin article that described the new warnings in the labeling and included the patient leaflet;

Asked manufacturers of generic propoxyphene products to produce the same patient leaflet and distribute it voluntarily with their products; and

Established a monitoring group in FDA to follow sales, abuse episodes, and deaths related to propoxyphene to determine whether the labeling, educational, and publicity efforts begun in August 1979 are accomplishing their goal.

In addition to these steps taken by us, the following commitments were made by Eli Lilly & Co.:

To use the Lilly sales force to contact personally 125,000 physicians identified as significant prescribers of propoxyphene products and to undertake a mailing program to an additional 115,000 physicians;

To update the physicians' labeling to include revised warnings on overdosage and use with alcohol or other central nervous system depressants or in depressed patients and to distribute this revised labeling in a brochure to physicians, dentists, and pharmacists;

To develop a patient leaflet with dosage instructions and warnings and distribute it through physicians, dentists, and pharmacists;

To distribute to pharmacists stickers to be placed on prescription vials that warn patients to consult with their physicians before taking propoxyphene with various central nervous system depressants and to use alcohol only in moderation;

To include in advertising for a 6-month period warnings on propoxyphene in the first page of all ads. To prepare a film on suicide and a booklet on management of propoxyphene overdosage for physicians, hospital staff, and emergency room personnel; and

Last, to provide quarterly reports to the FDA with summaries of evaluations of their educational campaigns via physician, pharmacist, and patient surveys as well as surveys of utilization and reports of abuse and deaths.

Since late 1978, following the petition to the Secretary, we have been accumulating data from a variety of sources on propoxyphene's role in abuse and deaths. Much of this has been summarized in the previous two quarterly reports to the Secretary.

This information has shown a steady decline in the prescribing of propoxyphene products. This decline began in about 1976 and is continuing to the present. An interesting measure of changing attitudes toward the prescribing of propoxyphene is reflected by the number of new prescriptions issued. Since January 1979 there has been a 22-percent decrease in new prescriptions for Lilly propoxyphene products from 1.21 million to 0.94 million new prescriptions per month. However, prescribing of the less frequently used, generic propoxyphene products has increased slightly, from 0.13 to 0.14 million prescriptions per month.

During the same period there has been some shift to other analgesics.

Associated with this decreased use of propoxyphene there is a continuing trend of decreased emergency room and crisis center visits which reflects misuse. Our data shows the monthly trend in consistently reporting emergency room mentions for propoxyphene from January 1976 through December 1979. In that time there has been a 35-percent decrease in emergency room mentions between

the fourth quarter of 1977 and the fourth quarter of 1979, with most of this occurring during 1979.

This downward trend is also reflected in our DAWN data on propoxyphene associated deaths from consistently reporting medical examiners. Here, however, there is a 9-month lag in reporting deaths so that data reflecting the impact of the Lilly informational campaign on deaths in the last quarter of 1979 will not be available until the fall of 1980. Nonetheless, there has been a 50-percent decrease in propoxyphene associated deaths reported between the second quarter of 1977 and the second quarter of 1979.

Lilly, at the request of FDA, has also arranged for a special survey of propoxyphene related deaths observed by 18 selected medical examiners nationwide. The results of this survey have been promised to the FDA by the end of this month.

In conclusion, Mr. Chairman, propoxyphene is widely used; it provides pain relief for many people. Although it is not a powerful analgesic, it has advantages for persons who cannot tolerate aspirin or acetaminophen. The FDA has a long and extensive experience with reviewing propoxyphene. In the past year such review has become almost continuous. We are pleased that there has been a significant decrease in the number of abuse episodes related to propoxyphene over the past 2 years and an apparent reduction in deaths. Because of the lag time in reporting deaths, however, it is still too early to know whether an additional incremental gain was achieved by the Lilly informational campaign and our own publicity efforts of last fall. In addition, we do not yet know the extent to which the patient leaflet has contributed, or will contribute, to the safer use of propoxyphene.

We are continuing to monitor the use, abuse, and misuse of propoxyphene carefully. If the downward trend in abuse rates and deaths does not continue, or new problems arise, I can assure you that appropriate regulatory action will be taken.

Mr. Chairman, I would be pleased to answer any questions you or other committee members may have.

[Testimony resumes on p. 110.]

[Dr. Goyan's prepared statement and attachment follow:]

STATEMENT

BY

JERE E. GOYAN

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Chairman:

pleased to represent the Department of Health and
n Services (HHS) at this hearing and to discuss our
vities with respect to propoxyphene.

GROUND

ropropoxyphene hydrochloride (DPX) and its
inations with aspirin, phenacetin, and caffeine were
marketed in 1957 under the brand name of Darvon
arvon Compound by the Eli Lilly Company. At that
the Federal Food, Drug, and Cosmetic (FD&C) Act
red only proof of safety, not of efficacy, as a
tion of FDA approval of a drug. After passage of
rug Amendments of 1962, which for the first time
red proof of efficacy, a panel of experts
lished by the National Academy of Sciences-National
rch Council (NAS-NRC) under contract to FDA
ed propoxyphene products and concluded they were
tive for the relief of pain. FDA subsequently, in
concluded that DPX was effective. New
yphene products containing the napsylate salt of

propoxyphene rather than the hydrochloride, either alone (Darvon-N) or in combination with acetaminophen (Darvocet-N) or aspirin (Darvon-N with ASA), were marketed in the early 1970's after approval of new drug applications. In recent years a number of generic propoxyphene-containing products have also been approved.

The combination products are clearly effective even though the contribution of their propoxyphene component may be relatively small. Propoxyphene has been marketed in an array of dosage forms, combinations, and salts that offer physicians a wide variety of options for managing patients with painful disorders. Many physicians believe that no other prescription analgesic possesses a combination of properties so attractive to the general physician for the management of patients with mild to moderate pain. It does not carry the risks of serious gastro-intestinal bleeding associated with aspirin, the liver damage associated with overdoses of acetaminophen, or the kidney damage associated with phenacetin. Neither does propoxyphene cause drowsiness or constipation to the same extent as codeine.

For many years propoxyphene-containing products have been among the most frequently prescribed prescription drugs in the United States. Appendix 1 shows the number of outpatient prescriptions written by year since 1964. Products containing propoxyphene peaked in popularity from 1973 to 1975 with retail prescriptions totaling over 39 million annually in those years. While the total number of prescriptions has dropped to some 31 million for 1978 and 25 million for 1979, propoxyphene products are still very popular. The following table shows the rank of each among the 200 most prescribed drugs for the years 1972 through 1979:

Rank Among the Top 200 Most Prescribed Drugs

	1972	1973	1974	1975	1976	1977	1978	1979
Darvocet-N	-	87	24	20	18	18*	12*	14*
Darvon 32 mg & 65 mg	35	47	68	71	78	93	123	164
Darvon Compound-65 APC	2	3	3	6	15	20	25	49

*Both Darvocet-N 100 and Darvocet-N 50 were included for the years 1972-1976. Data for 1977-1979 is for Darvocet-N 100 alone.

ABUSE OF PROPOXYPHENE

Propoxyphene is structurally related to the narcotic analgesic methadone. Although its general pharmacological properties are those of the narcotics as a group, the potency of propoxyphene hydrochloride is from 1/2 to 2/3 that of codeine. Compared with other prescription analgesics, the adverse reactions associated with propoxyphene are mild and infrequent when the drug is taken as directed in the absence of other CNS depressants and/or alcohol.

The abuse potential of propoxyphene was recognized as early as the late 1950's but was not a major public health concern until the late 1960's and early 1970's. Chronic use of high doses of propoxyphene can produce physical and psychological dependence that has characteristics similar to that associated with morphine-like drugs but is much lower in intensity and relatively much less common. Intravenous "street" use by drug abusers was once popular in the late 1960's, but this practice waned, partly because propoxyphene damages blood vessels and injures tissue at the injection site. Abuse of propoxyphene can

produce overdose deaths that resembled those seen with heroin and methadone i.e., characterized by respiratory depression and pulmonary edema.

The epidemiologic data on propoxyphene fatalities have consistently shown that the majority of deaths occurred because of deliberate overuse, abuse and suicide. If the ratio of all deaths reported to DAWN relative to prescription use according to the National Prescription Audit is calculated, the propoxyphene group of drugs rank third behind short-acting barbiturates and sedative hypnotics as a cause of deaths, as summarized in Appendix 2.

The FDA is not aware of any cases in which death was caused by propoxyphene products when taken alone in recommended doses and in which neither alcohol nor tranquilizers were also involved. There are, however, a number of "accidental" deaths which have apparently occurred as a result of the consumption of propoxyphene in quantities smaller than those used in suicide, yet still in excess of recommended therapeutic dosage and usually combined with alcohol and/or tranquilizers.

The mechanism of death in those cases is commonly attributed to respiratory depression, a typical action of narcotics, although cardiac toxicity of its metabolite norpropoxyphene has been suggested as a possible additional cause. Further research must be done to establish more clearly the cause of death in such cases and recent efforts are underway at the National Institute on Drug Abuse, with FDA advice, to begin developing standardized criteria for use by medical examiners and coroners in determining precise causes of death.

REGULATORY ACTIONS

At the outset of my discussion of regulatory actions, let me take a minute to review the scheduling process briefly. Before any scheduling action is undertaken, the Attorney General, after gathering the necessary data on abuse, requests scientific and medical evaluation by the Secretary of HHS. The recommendation of the Secretary to the Attorney General is binding on the Attorney General in the sense that DEA may schedule a drug only on recommendation of the Secretary and in a schedule no more restrictive than that recommended by the Secretary. The

Attorney General need not schedule a drug so recommended, however, and he or she may do so in a less restrictive schedule. In addition to regulation under the Controlled Substances Act (CSA), DPX, like other drugs is regulated under the FD&C Act.

In the past decade, in response to problems associated with abuse of propoxyphene products and misleading promotion on products, FDA has taken a number of actions:

-- In 1972, because of misleading statements on the effectiveness of Darvon made to physicians in a letter from Eli Lilly and Company, we required the manufacturer to issue a "Dear Doctor" letter stating: "There is no substantial evidence to demonstrate that 65 mg of Darvon (DPX-HCl) is more effective than 650 mg of aspirin (two 5-grain tablets), and the preponderance of evidence indicates that it may be somewhat less effective."

-- In April 1976, FDA's Controlled Substances Advisory Committee (CSAC) recommended that propoxyphene (and its salts and preparations) be controlled in Schedule IV of the CSA.

-- FDA and HEW concurred with the CSAC's recommendation, and DEA, therefore, in March 1977, placed propoxyphene, its salts and preparations, in Schedule IV of the Controlled Substances Act.

-- Labeling for propoxyphene was further revised in 1978 to add a warning against the additive depressant effect of the products when used in conjunction with alcohol, tranquilizers, sedative hypnotics, and other central nervous system depressants, and to require additional information on adverse reactions, drug interactions, and management of overdosage. A warning against use of the products during pregnancy was also added because of the danger of propoxyphene causing physical dependence in the fetus, leading to neonatal withdrawal syndrome.

RECENT MAJOR ACTIONS

On November 22, 1978, the Secretary of the Department of Health, Education, and Welfare was asked by the Health Research Group (HRG) to suspend approval of the NDA's for propoxyphene-containing products under section 505(e) of the Federal Food, Drug, and Cosmetic Act on the grounds that the continued marketing of these drugs represents an imminent hazard to the public health. HRG requested alternatively that if the Secretary did not suspend approval, he support HRG's petition to DEA to reschedule propoxyphene into Schedule II of the Controlled Substances Act.

This prompted a review by FDA of whether propoxyphene met the safety and effectiveness requirements of the Federal Food, Drug, and Cosmetic Act. On February 15, 1979, Joseph A. Califano, Jr., then Secretary of Health, Education, and Welfare, denied the HRG imminent hazard request because grounds for withdrawal of the new drug applications were felt to be lacking.

The Secretary also directed FDA to take the following actions:

- Distribute an FDA Drug Bulletin to physicians and health professionals advising of the risks associated with the use of and abuse potential of propoxyphene. An article was published in the February - March 1979 issue of FDA Drug Bulletin. The Drug Bulletin is mailed to more than a million health professionals in the U.S. (Propoxyphene also was the subject of articles in the May-July 1977 and March-April 1978 Drug Bulletins.)

- Disseminate information on the risks of propoxyphene to the public. An article, "Darvon Subject to Misuse," appeared in the March 1979 issue of FDA's official magazine, FDA Consumer, and more than half a million copies were reprinted and distributed through FDA's field offices; through the Consumer Information Center in Pueblo, Colorado; and in supermarkets across

the nation. In addition, update articles on Darvon appeared in FDA Consumer magazine in the July-August, October and November 1979 issues.

An earlier article that appeared in FDA Consumer in November 1976, entitled "Controls Urged on Top Rx Pain Drug," also had been reprinted and half a million copies distributed.

In March 1979, in conjunction with the article in FDA Consumer, FDA mailed to every radio station in the U.S. public service announcements on the dangers of propoxyphene abuse. And on July 30, 1979, FDA issued a press release on Lilly's plans to distribute a patient package insert on Darvon.

- Hold a hearing to allow the public an opportunity to present additional evidence on the benefits and risks of propoxyphene (held on April 6, 1979.)

- To complete by June 1979 the administrative process on the possible rescheduling of propoxyphene, including review by the Drug Abuse Advisory Committee (meeting held April 17, 1979).

Evidence was presented at the hearing of April 6, 1979 on both the safety and the efficacy of propoxyphene and the need for this drug in both acute and chronic medical conditions, especially in the treatment of arthritis. A meeting of the Drug Abuse Advisory Committee (DAAC) was also held on April 17, 1979 to consider the rescheduling of propoxyphene. After a detailed review and discussion, the DAAC recommended that propoxyphene remain in Schedule IV and that it be treated as a narcotic. Lilly representatives also offered at the meeting to conduct an informational campaign directed at physicians, pharmacists, and patients to warn of the abuse potential of propoxyphene and of the risks associated with the use of higher-than-recommended doses, especially when taken with alcohol or other CNS depressant drugs. This recommendation was later accepted by FDA because it was felt to address most directly the major problem associated

best copy available

with propoxyphene deaths - i.e., intentional overdosage or accidental death when propoxyphene is taken with alcohol or tranquilizers.

The Drug Abuse Advisory Committee considered the options of placing propoxyphene in either Schedule II or III of the CSA or leaving it in Schedule IV. The Committee's recommendation that propoxyphene remain in Schedule IV was based primarily on the fact that there was no significant new evidence presented to warrant a move from the schedule adopted in 1977, nor was rescheduling felt to be the optimal remedy to the problem of overdose deaths.

On June 15, 1979, the Secretary announced his conclusion that DPX should remain in Schedule IV, but indicated simultaneously his concern that propoxyphene may better satisfy certain of the legal criteria for Schedule II than for Schedule IV of the CSA. He also asked the Assistant Secretary for Health, to establish an Interagency Task Force made up of representatives of FDA, NIH and NIMH to summarize all pharmacologic data, epidemiology data, and outline new areas for needed research on the abuse

potential of propoxyphene. This task force is now preparing its final report for the Secretary.

The FDA also took the following actions at that time:

- Required all manufacturers of propoxyphene drug products to revise the physicians labeling to include the new warnings.
- Issued a second FDA Drug Bulletin article that described the new warnings in the labeling and included the patient leaflet. (September 1979).
- Asked manufacturers of generic propoxyphene products to produce the same patient leaflet and distribute it voluntarily with their products.
- Established a monitoring group in FDA to

follow sales, abuse episodes and deaths related to propoxyphene to determine whether the labeling, educational and publicity efforts begun in August 1979 are accomplishing their goal.

In addition, to these steps taken by the Government, the following commitments were made by Eli Lilly & Co., the major manufacturer, in a letter of June 7, 1979 to the Bureau of Drugs:

- To use the Lilly sales force to contact personally 125,000 physicians identified as significant prescribers of propoxyphene products and to undertake a mailing program to an additional 115,000 physicians.

- To update the physicians' labeling to include revised warnings on overdosage and use with alcohol or other central nervous system depressants or in

- To provide quarterly reports to the FDA with summaries of evaluations of their educational campaigns via physician, pharmacist and patient surveys as well as surveys of utilization and reports of abuse and deaths.

Since late 1978, following the petition to the Secretary, the FDA has been accumulating data from a variety of sources on propoxyphene's role in abuse and deaths. Much of this has been summarized in the previous Federal Register notice and the two quarterly reports to the Secretary. The information compiled includes studies of utilization, as well as data on deaths and morbidity. We have also requested specific studies of the clinical cardiotoxicity of propoxyphene and of deaths associated with propoxyphene seen in a specific group of coroners' offices.

This information has shown a steady decline in the prescribing of propoxyphene products. This decline began in about 1976 and is continuing to the present (Appendix 1).

depressed patients and to distribute this revised labeling in a brochure to physicians, dentists and pharmacists.

- To develop a patient leaflet with dosage instructions and warnings and distribute it through physicians, dentists and pharmacists.

- To distribute to pharmacists stickers to be placed on prescription vials that warn patients to consult with their physicians before taking propoxyphene with various central nervous system depressants and to use alcohol only in moderation.

- To include in advertising for a 6-month period, warnings on propoxyphene in the first page of all ads.

- To prepare a film on suicide and a booklet on management of propoxypnene overdosage for physicians, hospital staff and emergency room personnel.

An interesting measure of changing attitudes toward the prescribing of propoxyphene is reflected by the number of new prescriptions issued. Since January 1979, there has been a 22% decrease in new prescriptions for Lilly propoxyphene products, from 1.21 million to .94 million new prescriptions per month. However, prescribing of the less frequently used, generic propoxyphene products has increased slightly, from .13 to .14 million prescriptions per month. (Appendix 3).

During the same period there has been some shift to other analgesics. For example, from January to December 1979, there was a slight increase in new prescriptions for codeine (2%), pentazocine (7%), and because of its approval as an analgesic in August 1979, of ibuprofen, a non-steroidal anti-inflammatory analgesic (62%).

Associated with this decreased use of propoxyphene there is a continuing trend of decreased emergency room and crisis center visits which reflects misuse. Appendix 4 shows the monthly trend in consistently reporting emergency room mentions for propoxyphene from January 1976 through December 1979. There has been a 35% decrease in

emergency room mentions between the fourth quarter of 1977 and the fourth quarter of 1979, with most of this occurring during 1979.

This downward trend is also reflected in DAWN data on propoxyphene-associated deaths from consistently reporting medical examiners as shown in Appendix 5. Here, however, there is a 9-month lag in reporting deaths so that data reflecting the impact of the Lilly informational campaign on deaths in the last quarter of 1979 will not be available until the fall of 1980. Nonetheless, there has been a 50% decrease in propoxyphene associated deaths reported between the second quarter of 1977 and the second quarter of 1979.

Lilly, at the request of FDA, has also arranged for a special survey of propoxyphene-related deaths observed by 18 selected medical examiners nationwide. The results of this survey have been promised to the FDA by the end of this month.

The FDA has also monitored the performance of Lilly in conducting its informational campaign by using the IMS

National Detailing Audit verbatims. These verbatims are photocopies of forms filled out by practitioners after detail persons leave the practitioner's office.

The results of this survey have indicated that personal visits to physicians by Lilly representatives occurred mainly in August and September 1979, that generally less than half of each visit was devoted to its Darvon products, and that Darvon was on the average the second drug, not the first drug, mentioned. To our surprise, the informational campaign was also combined with a sampling program for Darvon products. Samples of Darvon products were left behind in nearly 50% of visits in August 1979, 60% of visits in September and more than 75% in October and November.

Because of these deficiencies, we have felt that Lilly has not yet met our expectation for a personal contact informational campaign intended solely to sensitize prescribers to the precautions necessary for the safe use of propoxyphene products. This opinion was conveyed to the Chairman of the Board of Lilly by the Director of the Bureau of Drugs in a letter on March 17, 1980. Lilly

representatives met with Bureau officials on this matter on April 24, 1980 and submitted a survey intended to show that physician recognition of the risks of propoxyphene is high. We are currently reviewing this material and will be meeting again with Lilly in the near future.

CONCLUSIONS

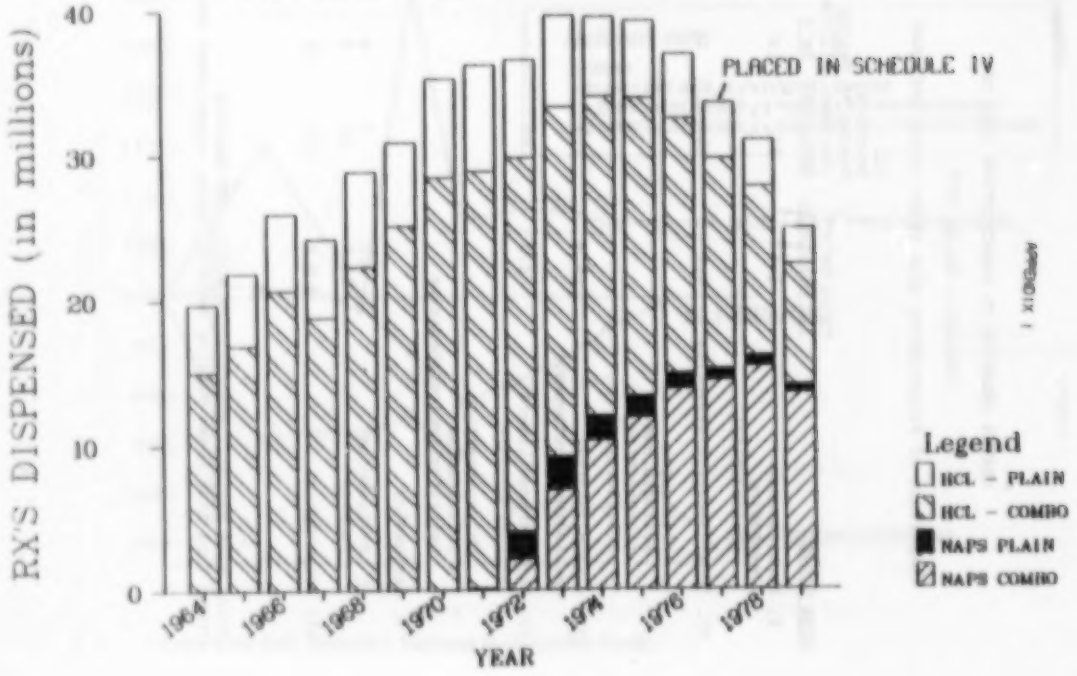
In conclusion, Mr. Chairman, propoxyphene is widely used; it provides pain relief for many people. Although it is not a powerful analgesic, it has advantages for persons who cannot tolerate aspirin or acetaminophen. The FDA has a long and extensive experience with reviewing propoxyphene. In the past year such review has become almost continuous. We are pleased that there has been a significant decrease in the number of abuse episodes related to propoxyphene over the past two years and an apparent reduction in deaths. Because of the lag time in reporting deaths, however, it is still too early to know whether an additional incremental gain was achieved by the Lilly informational campaign and our own publicity efforts

of last fall. In addition, we do not yet know the extent to which the patient leaflet has contributed, or will contribute, to the safer use of propoxyphene.

We are continuing to monitor the use, abuse, and misuse of propoxyphene carefully. If the downward trend in abuse rates and deaths does not continue, or new problems arise, I can assure you that appropriate regulatory action will be taken.

Mr. Chairman, I would be pleased to answer any questions you or other Committee Members may have.

PROPOXYPHENE USE BY SALT AND FORMULATION
TOTAL RETAIL RX'S DISPENSED
YEARLY - 1964 THROUGH 1979



APPENDIX I

APPENDIX 2

DEATHS RELATIVE TO PRESCRIPTION (Rx) USE

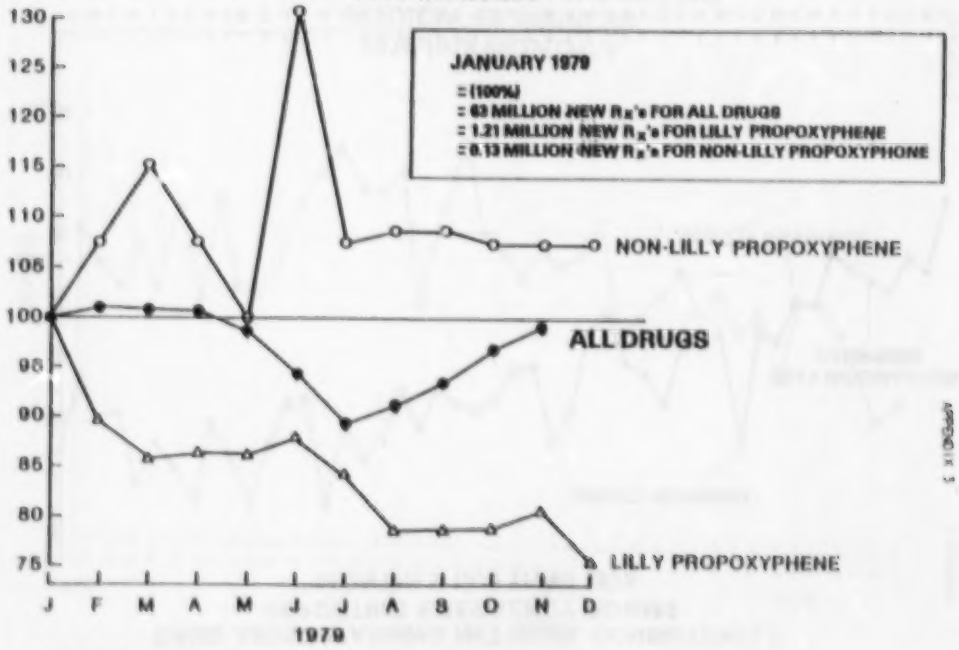
January - March 1979

Comparison of Propoxyphene with Other Drugs (NPA, DAWN)

Drug Group	Total Rx's* (in millions)	All Reported Deaths ** (Coroner Mentions)	Deaths MILLIon Rx's	Group Rank
I. Barbiturates (excluding phenobarbital)	1.5	221	147	1
II. Other Sedative/Hypnotics	4.4	115	26	2
flurazepam				
methaqualone				
glutethimide				
ethchlorvynol				
III. Benzodiazepines (excluding flurazepam)	15.9	117	7	6
IV. Major tranquilizers/ antidepressants	3.9	36	9	4
Chlorpromazine				
Thioridazine				
Amitriptyline/Perphenazine				
V. Analgesics				
Pentazocine	0.9	7	8	5
Codeine	13.0	81	6	7
VI. Propoxyphene	6.6	112	17	3

*Data from National Prescription Audit, IMS America
**Data from Drug Abuse Warning Network, NIDA, unpublished data.

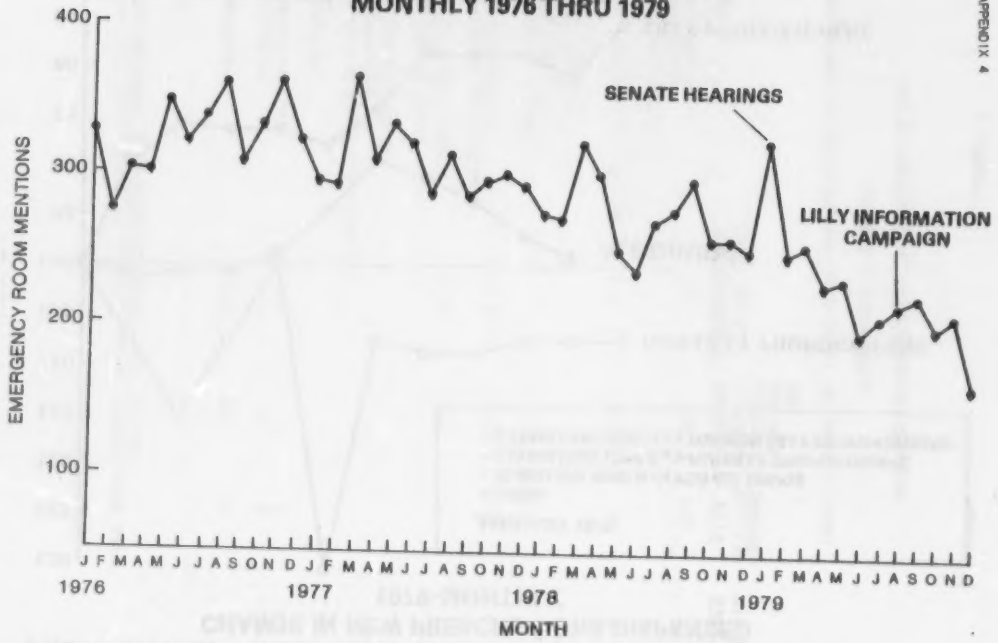
PROPOXYPHENE (LILLY vs. NON-LILLY) vs. TOTAL Rx|MARKET PERCENT CHANGE IN NEW PRESCRIPTIONS DISPENSED 1979-MONTHLY



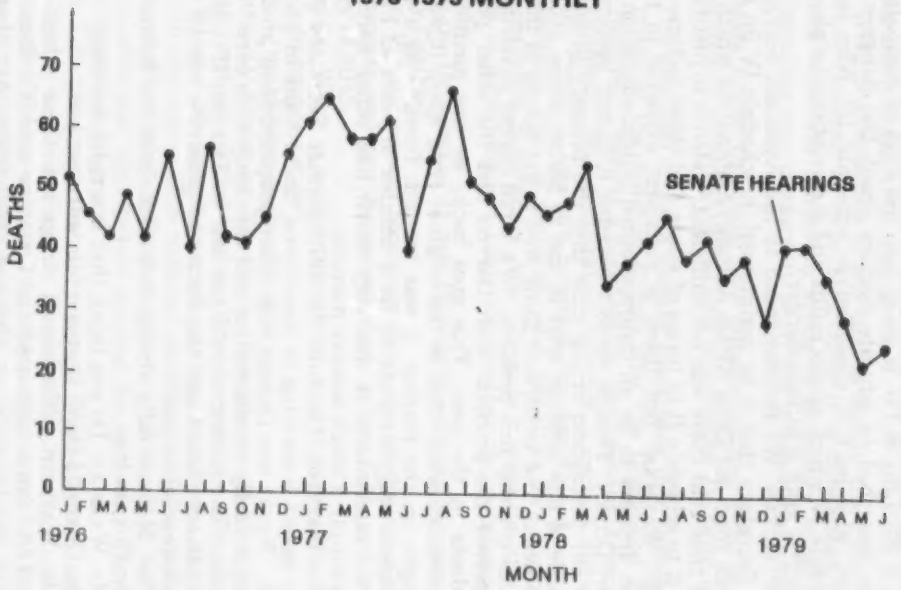
Data from IMS America's National Prescription Audit

APPENDIX 4

PROPOXYPHENE
DRUG ABUSE WARNING NETWORK CONSISTENTLY REPORTING EMERGENCY ROOMS
MONTHLY 1976 THRU 1979


400
300
200
100
EMERGENCY ROOM MENTIONS
SENATE HEARINGS
LILLY INFORMATION CAMPAIGN
J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D
1976
1977
1978
1979
MONTH

PROPOXYPHENE DEATHS
DAWN-CONSISTENTLY REPORTING
MEDICAL EXAMINERS
1976-1979 MONTHLY



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Mr. WAXMAN. Thank you, Dr. Goyan. I appreciate your testimony.

If FDA is spending money to advise the public of these dangers and if Eli Lilly & Co. is going into the kind of campaign that you have described to educate doctors about the dangers of Darvon abuse, why isn't it classified in schedule II? Why is it still in schedule IV which allows refills and prescriptions by phone which is evidently such a serious danger?

Dr. GOYAN. We recommended to the Assistant Secretary and to the Secretary that it be maintained in schedule IV on the basis of advice from our Drug Abuse Advisory Committee which believed at that time that there was not sufficient evidence to justify rescheduling it to schedule II in terms of abuse and other factors.

Mr. WAXMAN. But there is sufficient evidence to bring about what appears to be an unprecedented public education campaign?

Dr. GOYAN. That is correct because it is our perception and it was our perception at the time that the primary problem was use outside of our labeling; that is, use in higher doses, accidentally or by suicide. The important thing was to get across to the physicians of this country this problem. To a large degree physicians have not perceived the problem with Darvon and the other propoxyphene products in the past. This goes back, as was mentioned by the previous panelist, that in the original drug when it was originally brought on the market, it was brought forward as a nonnarcotic analgesic and that went on for a number of years as I am sure Dr. Carter remembers. It was very much like other narcotics and it was simply a much weaker narcotic.

Mr. WAXMAN. On June 15, 1979, former Secretary Joseph Califano issued a warning to Americans, and I want to quote what he said. "Never use Darvon and other propoxyphene products unless there is really no alternative and then only with care." He went on to add, "The patient should not ask for Darvon. If it is prescribed, the patient should ask the doctor to prescribe one of the equally effective alternatives."

That is an awfully strong statement from the former Secretary.

Dr. GOYAN. It is.

Mr. WAXMAN. Do you think that is a valid warning?

Dr. GOYAN. I think that is a fair warning, yes.

Mr. WAXMAN. Schedule II drugs are these which have been found to have a high potential for abuse and it's abuse may led to severe psychological or physical dependence. Are there drugs in schedule II for which there is the kind of educational campaign and strong warnings such as the kind we are getting for Darvon?

Dr. GOYAN. No, but on the other hand, I do not believe there are any drugs in schedule II that have given the extent of the problem that Darvon has.

Mr. WAXMAN. Maybe Ms. Buc can answer this question. What is the meaning of the U.N.'s action to place propoxyphene in schedule II of the international narcotics schedule and how does this action relate to our country's responsibilities to conform domestic regulatory policies to the 1961 Single Convention. Could you give us the background on that?

Ms. BUC. Under the Controlled Substances Act, the Attorney General must take whatever action is necessary to conform the

domestic scheduling to the U.N. action. That process is now under way as I understand it.

Mr. WAXMAN. What regulatory obligations has the United States incurred as a result of the U.N. action?

Ms. BUC. Well, that question is one that is within the discretion of the Attorney General. In general, I think it is understood that he has to take whatever minimum action is necessary to get the domestic scheduling into conformity with the international scheduling situation.

Mr. WAXMAN. Under the Controlled Substances Act, what is the practical regulatory effect of classifying a schedule IV drug as a "narcotic"?

Ms. BUC. The practical effect of putting something in schedule IV is across a range of the kinds of things that the Controlled Substances Act requires. There is a registration requirement, a record-keeping requirement, DEA registration number, a certain dispensing limitation. Prescriptions are required, for example, a certain amount of security that is required, and penalties are imposed under the Controlled Substances Act. There is a requirement for various kinds of export/import controls, whether the substance is narcotic or not.

Mr. WAXMAN. Dr. Goyan, do you believe the scheduling process is sufficiently flexible?

Dr. GOYAN. We have some concerns about the flexibility of the scheduling process and are discussing that in the FDA and with the Secretary of HHS.

Mr. WAXMAN. When can the committee expect to receive the Department's recommendation?

Dr. GOYAN. I would hope early next year.

Mr. WAXMAN. Dr. Crout, on March 17, 1980, you wrote Eli Lilly a letter strongly critical of their educational campaign directed at prescribers. When Lilly agreed to conduct this campaign, did they also agree with the use of IMS national detailing audit verbatims as a measure of effectiveness? Do you believe that the IMS verbatims are a reliable and appropriate method for assessing the Eli Lilly Darvon education program?

Dr. CROUT. I do not know that they agreed. We informed them that we were going to use it for that purpose. Yes, we continue to find them a useful means of assessing the performance of Lilly's detail persons in conducting that campaign.

Mr. WAXMAN. You also said in that same letter that the Lilly sales representatives violated the official position of the Pharmaceutical Manufacturers Association regarding provision of free samples of propoxyphene products. Do you know whether the Lilly representatives obtained written requests from the practitioners for these samples?

Dr. CROUT. They have clarified that subsequently. They did obtain written requests from the physicians during that sampling campaign. Now you may ask them. It is my understanding this simply means the physician signs a card or something on the spot and that a good deal of the sampling is detail-person-initiated rather than physician initiated. It is just impossible to tell how much is physician initiated in that setting.

Mr. WAXMAN. Are you now satisfied with the job that Eli Lilly is doing in its educational campaign?

Dr. CROUT. We have promised to get back to them and will do so very shortly on that. I think our letter to Mr. Woods still stands as outlining our concerns. Now they have come back to us and explained that from their point of view the most important thing is not how they did it but what the outcome is. They view the outcome measure as the survey of physician awareness which IMS has conducted and has been given to us, and I think we still have quite a difference of opinion on how to interpret that survey. They would look at what is called an aided responses by physicians; that is, the physician is asked the question: Do you know that Darvon should not be prescribed in patients who are addiction prone? A high percentage of physicians answer yes, up in the 80's and 90 percent. If, on the other hand, the answer is asked unaided, the percentages are quite low and somewhere between 15, 20, 25 percent of physicians will spontaneously point out the dangers of Darvon.

We are rather impressed with the low number of physicians who seem to spontaneously know in an unaided way what the warnings are associated with Darvon. Lilly is rather impressed with the high number that answer when aided. I think we continue to find that their way of looking at the problem is not a useful one from our point of view.

So I think we still do have a problem in trying to correct the awareness of physicians, considering it is a drug that has been promoted for 20 years, about the dangers associated with it. Now we are also assuming Lilly will be cooperative in doing that. They have indicated they will cooperate with our requests and the ball is at this moment in our court to get back to them on exactly what we want them to do.

Mr. WAXMAN. Thank you very much.

Dr. Carter.

Dr. GOYAN. I might add that it is important to realize that the IMS data is prepared primarily for pharmaceutical manufacturers; that is, they use it as a means of checking their own detailed persons. Apparently they believe in it and we believe it does a good job as well.

Mr. CARTER. Thank you, Mr. Chairman.

Dr. Goyan, are you satisfied with the present system for scheduling drugs under the Controlled Substances Act?

Dr. GOYAN. Well, it has certain problems and this is something that we intend to address early next year.

Mr. CARTER. Yes, sir. Are you satisfied with the position of Darvon in that schedule?

Mr. GOYAN. At the present time we are reconsidering the scheduling of propoxyphene on the direction of the Secretary of HHS and will be reporting to her about the middle of June.

Mr. CARTER. Yes, sir. In your studies on the use of propoxyphene have you found that the deaths result from propoxyphene alone or have they almost always included the use of alcohol or other drugs, such as tranquilizers?

Dr. GOYAN. In most cases they include either alcohol or other drugs but there are individual cases where there has only been propoxyphene primarily in the case of suicides.

Mr. CARTER. Yes, sir. How many capsules of Darvon could cause death? I believe the 65 milligram.

Dr. GOYAN. We estimate 20 to 30 capsules and that is not an unusual amount, as you know, Dr. Carter, in an individual prescription.

Mr. CARTER. That is quite true, but to take 20 of any tablet at the same time——

Dr. GOYAN. You have to be fairly intent.

Mr. CARTER. Yes, sir. It seems to me that the patient should recognize the danger of taking that many. That would be an attempt at suicide.

Dr. GOYAN. At times it is.

Mr. CARTER. If it were left up to you in this case, would you reschedule Darvon, propoxyphene?

Dr. GOYAN. As I said earlier, we are in the process of reconsidering that.

Mr. CARTER. All right, sir. We have another medicine which considerable work is being done on it at the present time called zomepirac, if I pronounce it correctly, and I believe it is a new drug.

Dr. GOYAN. Is that the new analgesic?

Mr. CARTER. Yes.

Dr. GOYAN. I know there is a new one.

Mr. CARTER. It is supposed to be as effective as morphine without the addictive properties.

Dr. GOYAN. I saw that in some of the earlier reports. However, I have to confess to a certain skepticism that is the same comment that was made about propoxyphene when it was first proposed.

Mr. CARTER. The same thing was said?

Dr. GOYAN. Yes.

Mr. CARTER. Do any of your aides know any more about zomepirac?

Dr. CROUT. Not on the spot. We could provide that for the record later if you would like, sir.

Mr. CARTER. I would like to know that.

[The following information was received for the record:]

NOTE.—Concerning Zomepirac—This drug is now in the investigational status and, therefore, no definitive information regarding its safety and effectiveness is available for it at this time.

Mr. CARTER. I would like to know if Dr. Wolfe has anything more on that.

Dr. WOLFE. It is illegal for the public to have anything on drugs that are being developed so I would know less.

Mr. CARTER. Illegal for the public to know about drugs that are under development?

Dr. WOLFE. Yes.

Mr. CARTER. This was written up in Reader's Digest.

Dr. WOLFE. If I asked the FDA for a list of the drugs, they would not give it to me.

Dr. GOYAN. If the public wants to know about a drug being tested——

Mr. CARTER. I have been in contact with a doctor who has been using that as an investigational new drug and spoke very highly of it. If it actually did have this quality of relieving pain and at the same time not causing addiction, it would be extremely helpful.

Dr. GOYAN. Of course we might still have the problem of suicide.

Mr. CARTER. Thank you very kindly.

Mr. WAXMAN. Thank you, Dr. Carter.

Mr. Leland.

Mr. LELAND. Thank you, Mr. Chairman.

Let me say I really appreciate this hearing, it has a lot to do with when I was in the State legislature when I tried to identify drugs that adversely effected human health. This is certainly one of those kinds of situations. I am very concerned about this, Dr. Goyan, and about the abuse of Darvon. I am not qualified nor prepared to say that I advocate banning the use of Darvon altogether but I am concerned about the testimony prior to Dr. Wolfe and the implications in terms of the loss of life, both from the abuse of it and for the purpose of suicide. As I understand it, even though there have been significant steps taken that have caused a decrease of the impact of the abuse of Darvon, there still are lives being lost because of the abuse or the misuse of Darvon.

Why is there so much hesitation to reschedule Darvon? It seems to me very apparent already that from some of the questions that were asked by the chairman and also Dr. Carter that we have enough substantive information available just to reschedule Darvon to schedule II already.

Dr. GOYAN. Well, there are a number of factors that have to be taken into account in that, Mr. Leland, and its abuse potentials and the totality was taken into account when the recommendation was made against rescheduling it. At that time, Secretary Califano spoke to the issue of the nonavailability of sufficient evidence with regard to psychic and physical dependence and that is something that is ongoing in terms of studies at the present time.

I noticed in Dr. Wolfe's statement that he suggested that one thing that could be done at this time would be to recommend to physicians throughout the United States that they write on the prescription "do not refill." That, as we both know as fellow pharmacists, would be one way of controlling it and almost having the same effect as it would in schedule II as the terms of the practical outlet.

Mr. LELAND. Is there any way that you can effect that as a policy? I realize that what Dr. Wolfe suggested was a voluntary effort to ask physicians to do that but as we know doctors, pharmacists, other people who are asked to do things voluntarily, if they are in the habit of doing just the contrary will usually follow their habit. What is it that we can do to get doctors to do it?

Dr. GOYAN. Well, I think we do have to depend primarily on an educational campaign of physicians but I think we also need to educate the public. That is one of the reasons I have been a strong advocate for patient package inserts. I think that leaflets of this nature can warn the patient in that particular case what many of us worry about the most and that is the accidental overdose. That way the patient is aware of the problem, will be much less likely to

be "hooked" on it or anything of that nature. We do not have the pure power. We do not have the legal authority to go beyond that.

Mr. LELAND. Dr. Goyan, this advertising campaign that I hear about, did you really invest a lot of faith in the campaign to overcome the problems that we are having with Darvon, both from your point of view and from the point of view of the company itself?

Dr. GOYAN. Well, the fact of the matter is that the problem is decreasing, now not as rapidly as most of us would like but it is going down. We will not know the answer to the question that you posed as to the effect of the Lilly campaign or our own efforts until late summer, early fall, when the reports come in.

Mr. LELAND. Well, what about the loss of lives that we are experiencing? Aren't we in somewhat of an emergency situation with the loss of lives or the harm that Darvon is doing to the people? Recognizing that we have made some progress, is it just that we have made some progress but we will have to suffer more before we can come to the point of looking at and rescheduling and limiting the use, thus curtailing some of the abuse of the Darvon?

Dr. GOYAN. Obviously we would all like to see it go more rapidly, but on the other hand if we were to take emergency action in the case of this nature, then it would be a precedent to do that in cases, I would assume, for all drugs and I do not think that is an appropriate approach.

Mr. LELAND. What about the incidence of abuse and the harm that Darvon is directly responsible for compared to other drugs? Can you just give me some comparison of the drugs that are being abused today and causing the harm to the human life? I ask in order that we can arrive at some conclusion about, you know, the real urgency of the matter. You know, in comparison.

Dr. GOYAN. That is the sort of thing I would prefer to do for the record so we would have it in better form.

[The following material was received for the record:]

The attached four tables describe various aspects of propoxyphene abuse compared to other abused drugs using data from the Drug Abuse Warning Network (DAWN).

Table 16 from the Second Quarterly Darvon Report compares a ratio of deaths (medical examiner mentions) per million prescriptions dispensed among several therapeutic categories of drugs. Propoxyphene falls third behind two groups of sedative/hypnotics.

Tables VI, VII, and VIII from the Third Quarterly Darvon Report compares emergency room and medical examiner mentions by age for propoxyphene, pentazocine and codeine respectively. These data are presented quarterly.

Table 16

DEATHS RELATIVE TO PRESCRIPTION (Rx) USE

January - March 1979

Comparison of Propoxyphene with Other Drugs (DAWN, MPA)

Drug Group	Total Rx's* (in millions)	All Reported Deaths** (Coroner Mentions)	Deaths Million Rx's	Group Rank
I. Barbiturates (excluding phenobarbital)	1.5	221	147	1
II. Other Sedative/Hypnotics	4.4	115	26	2
flurazepam methaqualone glutethimide ethchlorvynol				
III. Benzodiazepines (excluding flurazepam)	15.9	117	7	6
IV. Major tranquilizers	3.9	36	9	4
Chlorpromazine Thioridazine Amitriptyline/Perphenazine				
V. Analgesics				
Pentazocine	0.9	7	8	5
Codeine	13.0	81	6	7
VI. Propoxyphene	6.6	112	17	3

*Data from National Prescription Audit, IMS America
**Data from Drug Abuse Warning Network, NIDA, unpublished data.

Table 37. MORBIDITY AND MORTALITY ASSOCIATED WITH PROPOXYPHENE: DRUG ABUSE WARNING NETWORK (DAWN) EMERGENCY ROOM MENTIONS* AND MEDICAL EXAMINER MENTIONS** ASSOCIATED WITH ALL PROPOXYPHENE PRODUCTS AND RELATIONSHIP TO PRESCRIPTIONS DISPENSED

	1/76	2/76	3/76	4/76	1/77	2/77	3/77	4/77	1/78	2/78	3/78	4/78	1/79	2/79	3/79	4/79	1/
Emergency Room (ER) Mentions*																	
Age 20	234	233	227	240	244	225	192	231	222	166	183	171	219	157	137	150	
20-39	530	559	616	625	568	595	569	526	516	519	625	495	502	397	402	335	
40-59	126	149	140	140	126	130	116	123	112	109	121	94	100	98	98	109	
60	11	27	27	21	20	18	30	20	24	30	24	22	21	20	24	20	
Total	912	792	1024	1035	968	975	906	909	869	821	861	790	847	674	684	616	
ER Mentions per million Rx's	97.4	84.5	113.4	113.9	115.6	110.8	110.3	112.3	106.9	107.7	114.1	104.9	128.4	103.7	111.9	105.9	
% of all ER Mentions***	2.4	2.0	2.5	2.6	2.5	2.5	2.3	2.4	2.3	2.2	2.3	2.2	2.3	1.9	1.9	1.8	
Medical Examiner (ME) Mentions**																	
Reported Cause																	
Suicide+	42	55	51	49	62	61	67	58	53	57	50	37	41	48			
Accidental	48	48	32	52	66	49	48	70	43	35	41	33	32	22			
Other	36	27	29	31	26	35	30	36	32	40	26	25	34	19			
Age 20	9	5	10	10	12	6	4	11	5	11	6	7	14	9			
20-39	72	76	61	75	86	91	102	68	83	66	71	61	57	53			
40-59	75	62	55	57	58	38	40	38	26	28	32	20	28	22			
60	10	7	3	10	18	17	7	5	13	5	8	7	8	7			
Total	126	130	112	132	164	145	153	122	128	107	117	95	107	88			
Deaths per million Rx's	13.5	13.9	12.4	14.5	19.6	16.5	18.6	15.1	15.5	13.4	15.5	12.6	16.2	13.7			
% of all ME Mentions****	4.9	5.0	4.7	5.9	7.4	6.8	6.9	6.1	6.0	5.1	6.4	4.9	5.0	4.0	6.1	5.5	
Utilization																	
National Prescription Audit**																	
New Rx's (000)											4355	4313	3749	3597	3342	3253	
Total Rx's (000)	9367	9370	9039	9089	8377	8802	8212	8097	8236	7625	7585	7533	6598	6497	5933	5817	5

*Emergency room mentions include all recorded visits to GPO consistently reporting emergency rooms where propoxyphene was mentioned, either alone or in combination with other drugs and/or alcohol, and was associated with or incidental to reason for visit.

**Medical examiner mentions include all deaths reported by 66 consistently reporting medical examiners associated with the presence of propoxyphene, either alone, in combination with other drugs and/or alcohol, associated causative or incidental to cause of death.

***ER mentions for propoxyphene ÷ ER mentions for all drugs.

****ME mentions for propoxyphene ÷ ME mentions for all drugs.

+Criteria for diagnosis of suicide vary.

**National Prescription Audit, IMS America, Ambler, PA.

Table XII : MORBIDITY AND MORTALITY ASSOCIATED WITH PENTAZOCINE, ONE TABLE WITHIN 10 YEARS (1970)
EMERGENCY ROOM MENTIONS* AND MEDICAL EXAMINER MENTIONS**
MENTIONED WITH ALL PENTAZOCINE PRODUCTS AND RELATIONSHIP TO PRESCRIPTIONS DISPENSED

	1/75	2/75	3/75	4/75	1/77	2/77	3/77	4/77	1/79	2/79	3/79	4/79	1/81	2/81	3/81	4/81	1/83
Emergency Room (ER) Mentions*																	
Age 25	38	37	21	30	37	39	35	37	39	37	32	38	33	39	33	32	
25-29	110	142	114	125	163	172	156	162	202	203	218	228	241	212	265	257	
30-39	58	60	53	35	68	45	83	37	95	85	53	85	53	35	35	37	
40	6	6	7	5	9	6	5	6	5	7	7	7	10	2	10	1	
Total	192	245	217	195	229	240	269	233	233	275	330	328	336	278	332	332	
ER Mentions per million Rx's	121.1	158.5	215.3	194.6	221.0	232.3	256.9	216.2	205.0	243.9	302.3	327.6	307.5	253.0	306.8	307.8	
% of all ER Mentions***	0.5	0.6	0.6	0.5	0.6	0.6	0.7	0.6	0.7	0.7	0.9	0.9	0.8	0.6	1.0	0.9	
Medical Examiner (ME) Mentions**																	
Reported Cause																	
Suicide+	5	5	4	1	3	4	1	4	1	2	4	1	2	1			
Accidental	5	3	2	1	3	4	5	17	4	5	4	4	3	5			
Other	1	3	1	1	0	4	10	4	-	1	4	7	5	4			
Age 25	2	0	0	0	0	2	1	3	0	1	0	0	1	0			
25-29	4	7	5	2	4	10	12	20	8	6	12	5	9	10			
30-39	4	4	2	1	3	2	3	2	2	4	2	3	2	3			
40	2	0	1	1	1	1	0	2	2	0	1	1	0	0			
Total	12	11	7	4	8	21	16	27	12	11	15	9	12	13			
Deaths per million Rx's	12.5	9.8	6.4	5.0	5.8	20.1	11.3	21.3	6.2	8.2	14.8	15.0	12.3	15.1			
% of all ME Mentions****	0.5	0.4	0.3	0.4	0.3	1.0	0.7	1.4	0.5	0.4	0.6	0.7	0.5	0.7			
Utilization																	
National Prescription Audit++																	
Rx's (x 1,000)													530	537	555	519	505
Total Rx's (000)	1528	1113	1101	1002	1027	1055	1047	1065	1020	1038	970	936	995	859	931	881	

*Emergency room mentions include all recorded visits by 525 consistently reporting emergency rooms where pentazocine was mentioned, either alone or in combination with other drugs and/or alcohol, and was associated with or incidental to reason for visit.

**Medical examiner mentions include all deaths reported by 66 consistently reporting medical examiners associated with the presence of pentazocine, either alone, in combination with other drugs and/or alcohol, associated, causative or incidental to cause of death.

***428 mentions for pentazocine + 28 mentions for all drugs.

****80 mentions for pentazocine + 80 mentions for all drugs.

+Criteria for diagnosis of suicide vary.

++National Prescription Audit, IMS America, Ambler, PA.

Table 9111: [illegible] ASSOCIATED WITH CODEINE - DAWN DRUGS WORKING REPORTS (cont)
CHRONOLOGY DRUGS (NARCOTIC) AND MEDICAL EXAMINERS REPORTS**
ASSOCIATED WITH ALL CODEINE PRODUCTS AND RELATIONSHIP TO PRESCRIPTIONS DISPENSED

	1/75	2/75	3/75	4/75	1/77	2/77	3/77	4/77	1/78	2/78	3/78	4/78	1/79	2/79	3/79	4/79
Emergency Room (ER) Mentions*																
Age 25	107	133	133	130	117	104	127	125	130	103	125	116	115	110	130	130
25-59	693	627	654	639	650	604	676	625	529	493	571	676	561	577	630	665
60-59	86	101	112	106	109	103	124	123	108	132	125	120	113	105	95	105
60	17	10	16	29	24	12	11	27	27	21	23	25	25	11	16	9
Total	867	882	731	674	730	720	746	796	793	754	886	741	815	753	742	750
ER Mentions per million Rx's	57.9	58.9	48.8	45.1	48.3	47.5	49.1	44.1	50.6	47.7	45.7	43.3	47.8	45.4	44.5	46.3
% of all ER Mentions***	1.3	1.1	1.0	1.1	1.0	1.0	1.0	2.1	2.1	2.2	2.3	2.2	2.2	2.2	2.2	2.2
Medical Examiner (ME) Mentions**																
Reported Cause																
Suicide+	16	13	16	15	32	19	29	29	32	29	18	29	32	18		
Accidental	33	21	27	47	41	39	45	46	45	31	33	35	13	17		
Other	4	15	5	9	11	19	13	15	19	14	22	26	1	13		
Age 20	1	2	2	3	2	4	7	7	7	5	5	7	5	1		
20-39	35	29	26	46	38	45	56	57	52	45	51	53	37	43		
40-59	15	16	14	16	27	23	28	23	27	29	19	19	21	15		
60	4	3	6	7	7	3	9	8	5	1	6	10	5	3		
Total	51	49	48	72	74	72	79	88	88	75	79	89	68	64		
Deaths per million Rx's	4.5	4.2	3.8	6.3	6.1	6.2	6.3	6.6	7.3	5.9	6.1	6.3	8.9	8.1		
% of all ME Mentions****	2.0	1.9	1.9	3.2	3.1	3.6	3.8	4.8	4.8	3.7	4.3	4.6	4.1	3.5		
Utilization																
National Prescription Audit**																
New Rx's (000)																
Total Rx's (000)	11357	11505	12023	11866	11975	12140	12565	12393	11201	12551	12573	12561	12000	12057	12011	12034
													12000	12050	11812	11835

*Emergency room mentions include all recorded visits to 675 consistently reporting emergency rooms where codeine was mentioned, either alone or in combination with other drugs and/or alcohol, and was associated with or incidental to reason for visit.

**Medical examiner reports include all deaths reported by 50 consistently reporting medical examiners associated with the presence of codeine, either alone, in combination with other drugs and/or alcohol, associated causative or incidental to cause of death.

***639 mentions for codeine & 19 mentions for all drugs.

****80 mentions for codeine & 19 mentions for all drugs.

+Criteria for diagnosis of suicide vary.

++National Prescription Audit, IMS America, Ambler, PA.

Dr. GOYAN. I would point out that some analgesics and codeine rank fifth and seventh in terms of death in the United States.

Mr. LELAND. What is third?

Dr. GOYAN. Darvon.

Mr. LELAND. How are they classified? Where are they on the schedule?

Dr. GOYAN. Barbiturates are No. 2 and acetaminophen is in 4, or is it 2? They differ, the ones that are put together.

Mr. LELAND. Why would there be a suggestion that we skip schedule III to go to schedule II with Darvon?

Dr. GOYAN. Well, it is a question that schedule II is much more restrictive than schedule III and that that was the original suggestion of the Health Research Group and that is why people focused in on going to schedule II. How much improvement there would be in the problem by going to schedule III is unclear to me because of the fact that it would still allow five refills over a 6-month period. It does not change that.

Mr. LELAND. Let's not talk about schedule III, let's go from schedule IV to schedule II. It seems to me that because of the serious implications given—I forget which drugs he said was No. 3 or No. 2 in terms of abuse.

Dr. GOYAN. That whole series of sedatives.

Mr. LELAND. If these drugs are harmful to the human beings, why is it that we are so reticent to remove them?

Dr. GOYAN. Because we have to go by the test that is written into the law and that comes back in a way to the chairman's earlier question as to the problems that might reside in the scheduling legislation.

Mr. LELAND. I understand that. Now you said you are going to consider proposing advice to the Congress as to what kind of legislation is needed to diminish some of these problems the first of the year. What about the number of people who suffer from now until then? It seems to me that this is a terribly urgent situation and that we ought to address ourselves to these problems right away.

Dr. GOYAN. I agree it is a serious problem. I think we have enough problems including tranquilizers and antibiotics.

Mr. LELAND. I understand. It seems to me that if those problems are so prevalent—and I understand that we have limited resources, even the Congress cannot resolve the many problems that we have—but it seems to me that we ought to be able to at least address ourselves to the urgency of the matters to some degree. For instance, just rescheduling a drug that we know is considerably dangerous to the human life.

Dr. GOYAN. As I mentioned earlier, we are in the process of reconsidering the scheduling at this time for a recommendation to the Secretary.

Mr. WAXMAN. Thank you, Mr. Leland.

Mr. Luken.

Mr. LUKEN. Just one area on the positive side, if there is any. On the question of benefits, your written testimony is to the effect that many physicians believe that there is really no other prescription or analgesic which possesses the combination of properties which are attractive to the general physician for patients with mild or moderate pain.

Does that mean that there is a credible body of expert opinion that this drug has benefits, that it is useful?

Dr. GOYAN. Certainly there are many physicians who believe it is still a useful analgesic.

Mr. LUKEN. In fact it means that it has almost some unique qualities?

Dr. GOYAN. I do not think its uniqueness is because of its pharmacological characteristics but because it has been on the market longer than the other. It therefore most commonly comes to mind to the physician when he is confronted with the problem of a patient who has already taken aspirin, has come to him and asked for relief. He is looking for something. He does not want to go to the opiates or to the morphine-like drugs and decides that instead he will take something intermediate and that becomes Darvon.

Mr. LUKEN. You say it does not carry the risks of some of the other alternatives, gastrointernal bleeding or kidney damage, is that right?

Dr. GOYAN. It does not carry some of the risks of the three over-the-counter drugs that I have mentioned in the testimony.

Mr. LUKEN. So it has a certain utility as a result?

Dr. GOYAN. Yes.

Mr. LUKEN. That is all. Thank you, Mr. Chairman.

Mr. WAXMAN. Thank you very much.

Mr. LELAND. Mr. Chairman, I would like to ask another question.

Mr. WAXMAN. Please keep it brief.

Mr. LELAND. Mr. Crout, I just would like to ask you this. You said something about giving doctors warning or educating doctors of the dangers of prescribing Darvon to patients who are prone to addiction. Can you expound on that just a little bit for me, please?

Dr. CROUT. The critical warnings that we wanted to get across to the medical profession are that the drug should not be prescribed to patients who are addiction prone. It should be prescribed with great caution to patients who are alcoholic or drink too much. It should be given with a warning not to drink and it should be prescribed with great caution in patients who are also on tranquilizers. Now we have to give some flexibility to a doctor in individual situations. We have not absolutely proscribed its use with alcohol and tranquilizers but we want to get across the message that that is a red flag. Those messages are, so far as we can tell, still spontaneously recognized, still recognized by only a minority of the physicians who use Darvon, who prescribe Darvon, and it is that educational gap we want to keep working on.

Mr. LELAND. I understand. I was a bit confused by what you meant by patients who were prone to addiction.

Dr. Goyan, do you advise doctors put "do not refill" on prescriptions or not, yes or no?

Dr. GOYAN. I am not going to say yes or no, I am going to think about it.

Mr. LELAND. What office are you running for?

Dr. GOYAN. Commissioner of Food and Drugs.

Mr. WAXMAN. I appreciate very much you and your colleagues being with us and testifying before the subcommittee this morning.

Dr. GOYAN. Thank you very much, Mr. Chairman.

Mr. WAXMAN. Our next witness is Dr. Robert H. Furman, vice president, corporate medical affairs, Eli Lilly & Co. He is accompanied by Mr. Eugene Step, president, Pharmaceutical Division and Mr. Edgar G. Davis, vice president Corporate Affairs Division.

Dr. Furman, we have a copy of your prepared statement and that statement will be included in the record in its entirety. If you would, please summarize your statement so we will have an opportunity for questions.

STATEMENT OF ROBERT H. FURMAN, M.D., VICE PRESIDENT, CORPORATE MEDICAL AFFAIRS, ELI LILLY & CO., ACCOMPANIED BY EUGENE L. STEP, PRESIDENT, PHARMACEUTICAL DIVISION; AND EDGAR G. DAVIS, VICE PRESIDENT, CORPORATE AFFAIRS DIVISION

Dr. FURMAN. Mr. Chairman and members of the committee, I am Robert Furman, vice president of corporate medical affairs, Eli Lilly & Co. With me today are Mr. E. L. Step, president of the company's pharmaceutical division, and Mr. E. G. Davis, vice president of corporate affairs. In addition, I would like to introduce Dr. Arthur Scherbel, head of the Department of Rheumatology, Cleveland Clinic; Dr. Bryan Finkle, director of the Institute for Human Toxicology, University of Utah; and Mr. Frank Osgood, president, IMS America whose company provides the information to DEA on which the DAWN report is based and also has done the script audit on which assessments of educational programs and detailing successes have been carried out. These people have volunteered their services. They represent a very valuable resource and I hope you and the members of your committee will feel free to call on them.

Mr. WAXMAN. We appreciate their attendance.

Dr. FURMAN. We appreciate the committee's invitation to testify. In our statement we will provide information on the significant decline in the misuse of propoxyphene, the elements in the Lilly and FDA programs that have contributed to this result, and reassurance to the committee that propoxyphene, when used as recommended, is a safe and effective analgesic agent.

In 1975 the State toxicologist of North Carolina, Dr. Arthur McBay, provided information based on a systematic analysis of drug deaths throughout coroners' offices in that State which indicated an increasing number of deaths, primarily suicides, involving propoxyphene, either alone or in combination with other drugs. Lilly medical personnel met with Dr. McBay and, in consultation with FDA, requested Dr. Bryan Finkle to undertake a broader evaluation of medical examiner records at various sites throughout the United States. This evaluation was based on the analysis of more than 1,000 medical examiner cases involving propoxyphene, either alone or in combination with other drugs. The results of the evaluation were shared with FDA and DEA and published in 1976.

Lilly, working with FDA, revised the labeling of its Darvon products in 1976 and communicated new information applicable to the use of those products to members of the medical profession, both in a special brochure and in publication of a synopsis of Dr. Finkle's study in the Journal of the American Medical Association.

After evaluating data from Dr. Finkle's study, the FDA Controlled Substances Advisory Committee recommended that propox-

yphene be placed in schedule IV of the Controlled Substances Act. Subsequently, the Drug Enforcement Administration placed propoxyphene in schedule IV early in 1977. Lilly did not oppose this action.

As the result of a petition filed by the Health Research Group in late 1978, asking that propoxyphene be banned as an "imminent hazard" or be placed in schedule II, the Department of HEW and the Drug Enforcement Administration conducted a full and complete review of propoxyphene during the first 6 months of 1979. The Health Research Group petition contained no new scientific data but was based in large measure on:

One, information developed by Lilly in 1975 on toxicity associated with the misuse of propoxyphene.

Two, medical examiner reports reflected in drug abuse warning network data, that is, information comparable to that developed by Lilly in the 1975 Finkle survey.

The 1979 review examined all aspects of propoxyphene: its pharmacology, safety, effectiveness, and dependence liability. The evidence demonstrated that propoxyphene is both safe and effective when used as directed, that the drug has little potential to produce dependence, and that the principal form of misuse involves suicide or other self-destructive behavior that cannot be dealt with effectively through schedule II controls.

After extensive review, HEW determined in September of last year that there was insufficient evidence to reschedule the drug to schedule II of the act as HRG had proposed. Also, it was decided that the type of misuse which was occurring with propoxyphene could be reduced most effectively by providing information on proper use to physicians, pharmacists, and patients. These programs were initiated and are monitored by the Department of Health and Human Services.

The recent U.N. decision should not have any effect on the careful decision made in the United States last year. We believe the Commission's decision was unwarranted and we are hopeful that the United States and other nations will institute proceedings to obtain review or reconsideration of it.

The international decisionmaking process was cursory at best and cannot be compared with the careful consideration given to the scientific and medical issues in this country.

The American representatives on the World Health Organization committee that advised the Commission on narcotic drugs have stated that they understood that a decision to place propoxyphene in schedule II under the Single Convention would have no effect on its status under U.S. law.

The advice we have received from experts in international law indicates that they are right. The controls applicable to the schedule IV of the CSA, we are informed, are sufficient to meet the nation's obligation under the Single Convention. The Commission's decision, therefore, need not require any change in the carefully considered decision already made by Government authorities in the United States.

With respect to Dr. Wolfe's comments on the alleged abuse in other countries, I would like to point out that the United Kingdom opposed the Commission on Narcotic Drugs action, so did West

Germany, Austria, and India. Canada and Finland did not think scheduling was justified. The Commission on Narcotics Drugs Report to the Economic and Social Council, paragraph 118 states as follows:

> The representative of the Federal Republic of Germany stated that dextropropoxyphene was used in small quantities in medical preparations and that there was no need to place it under control. The representatives of India and the United Kingdom and the observer for Austria shared that point of view, since there was no abuse of substance in their countries. The observers for Canada and Finland also did not think that scheduling was justified, although they mentioned cases of abuse, especially in combination with alcohol. Measures had been taken at the national level . . . . Several speakers mentioned the need to control the substance as a gesture of international solidarity, even when abuse was reported in only certain states. . . .

As indicated in the introduction to this statement, we are pleased to report that misuse of propoxyphene is declining at a substantial rate. Let me point out several items.

First, that the exhaustive HEW/DEA investigation in 1979 reaffirmed the safety and effectiveness of propoxyphene when used as recommended.

Second, the improper use of propoxyphene is generally in association with multiple drug misuse, frequently with alcohol. It is a multiple drug, polydrug problem.

Third, when propoxyphene is misused, such misuse usually occurs with suicidal intent.

Lilly carefully monitors reports of the improper use of propoxyphene. This is done in several ways. Two of the most important sources of data have been the Drug Abuse Warning Network (DAWN), sponsored by the Drug Enforcement Administration, and the data collected directly from medical examiners by Dr. Finkle.

The DAWN system provides a number of measurements of drug abuse. Especially important are data from those medical examiners and coroners' offices which consistently report drug-induced deaths to the DAWN system.

From these data it is possible to tabulate the principal drugs mentioned in medical examiner cases, as well as to determine whether or not the death was "drug induced." I should note that it is not necessary for a specific drug to have been the actual cause of death for it to be "mentioned" in the DAWN reports. As we noted earlier, propoxyphene cases usually involve polydrug abuse, often with alcohol. As Secretary Califano said, "Under the DAWN reporting system, mentions of propoxyphene as related to death can mean that the deceased person had the drug in his or her blood."

When the data are examined for propoxyphene for the period 1976 through the third quarter of 1979, two very significant facts are evident.

One, since the various FDA and Lilly educational efforts for physicians and health professionals were initiated in the spring of 1979, there has been a 30-percent decline in propoxyphene mentions in medical examiner cases.

Two, there has been a 55-percent decline in propoxyphene mentions in medical examiner cases since the first quarter of 1977.

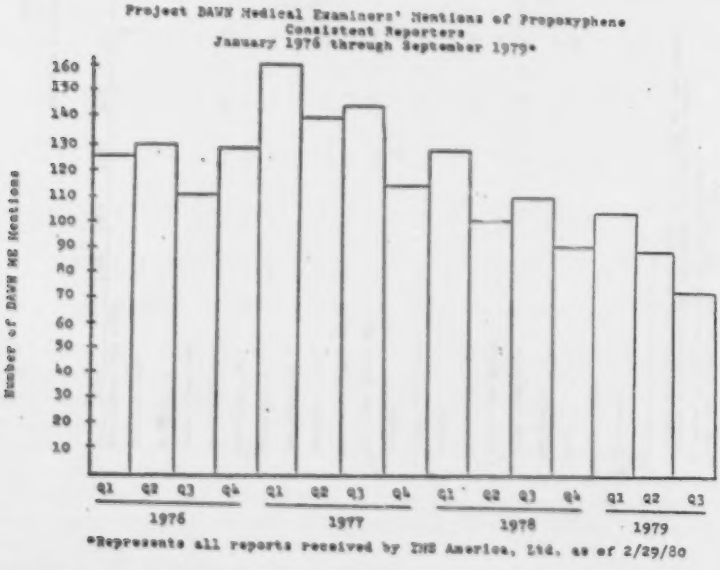
The actual number of quarterly propoxyphene mentions from consistently reporting medical examiners is listed below in table I.

TABLE 1.—*DAWN-M.E. mentions of propoxyphene*

Year and quarter:	
1977:	
1	162
2	140
3	145
4	116
1978:	
1	128
2	102
3	112
4	92
1979:	
1	105
2	89
3	73

Dr. FURMAN. You will find that a glance at the bar graph, graph I, will show that, since the first quarter in 1977 when the nonmedical examiner mentions peak, there has been a very gratifying and steady decline.

GRAPH I



Dr. FURMAN. Dr. Finkle who is with us this morning has also continued an in-depth examination of case data at medical examiner offices throughout the country. He informs me this morning that it is now complete. His data base now includes information

through 1979. His commentary on these cases as reported to FDA recently by Lilly is contained in appendix 1.

This information indicates decreased deaths involving propoxyphene for the period 1977 through 1979.

The data from Dr. Finkle's tabulation are in table II. I won't go through this. We will provide the committee the complete tabulation. Suffice it to say, a good many of these medical offices now have a substantial reduction in propoxyphene related deaths in comparison with 1977.

TABLE II

NUMBER OF PROPOXYPHENE-ASSOCIATED CASES

Site	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	Total*	No. of Cases Per Million Population**
Los Angeles City & Cty.	...	...	...	37	33	63	55	101	121	64	32	286	45.4
New York City	...	...	...	...	...	...	...	14	16	3	12	33	56.0
Buffalo	...	...	...	...	...	...	...	17	13	7	10	37	42.7
State - Maryland	...	...	...	...	...	...	56	46	58	65	31	169	50.0
State - Virginia	...	...	...	...	...	...	...	10	4	6	11	20	31.0
Washington, DC	...	...	...	...	...	...	...	6	3	2	7	11	24.0
Rhode Island	...	...	...	...	...	...	...	16	19	10	6	45	51.0
San Francisco	...	...	...	...	...	...	...	19	16	15	12	50	86.7
Phoenix	...	...	...	...	...	...	...	17	20	15	6	52	44.6
Las Vegas City & Cty.	...	...	...	2	1	2	7	6	10	1	1	17	45.0
San Diego City & Cty.	...	...	...	20	24	23	25	28	30	21	14	79	25.2
Oakland	...	3	3	3	9	11	5	9	20	10	10	39	49.0
Orange Cty., Calif.	...	...	...	8	12	18	17	19	26	14	13	59	40.0
Memphis	...	...	...	...	...	...	...	8	7	6	2	21	25.6
Dallas City & Cty.	...	...	...	16	10	16	27	12	19	16	14	47	50.8
State - New Mexico	...	...	...	...	4	8	10	12	10	11	5	33	34.5
State - Georgia	...	1	1	5	6	6	7	10	15	6	11	31	7.6
San Antonio	...	...	...	...	...	...	...	11	8	8	4	27	34.0
Miami	...	...	...	2	13	10	19	6	14	11	3	31	22.7
State - Utah	...	...	...	...	7	11	8	17	10	17	3	52	42.3
Pittsburgh	...	...	...	...	...	...	...	8	4	4	...	16	8.9

*Total for 1976, 1977, 1978, which is total base for the report.
**Based on 1980 estimated population; includes 1979 cases.
***Number of 1979 cases for ACP not available.
...=No data available; 0=no cases that year.

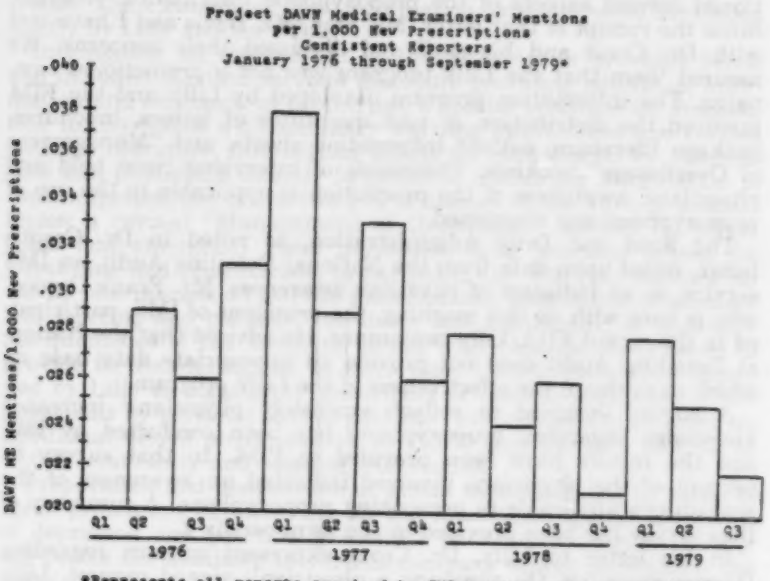
NUMBER OF PROPOXYPHENE-ASSOCIATED CASES (CONTINUED)

Site	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	Total*	No. of Cases Per Million Population**
Wayne Cty./Detroit	...	...	...	0	12	31	42	29	30	27	24	86	41.5
State - North Carolina	2	3	2	21	21	29	50	34	36	31	18	101	21.3
State - Illinois	...	...	...	...	...	...	...	...	48	44	18	92	20.1
Minneapolis	...	...	...	1	2	3	3	1	4	0	0	5	1.3
Philadelphia	...	...	...	25	22	20	18	26	29	20	17	83	52.6
U.S. totals	2	7	11	146	176	257	355	402	590	442	266	1522	32.0
Toronto & Ontario	...	...	...	44	39	46	42	77	113	111	83	301	46.3
Survey totals	2	7	11	190	215	303	397	559	711	583	369	1823	33.8

*Total for 1976, 1977, 1978, which is total base for the report.
**Based on 1980 estimated population; includes 1979 cases.
...=No data available; 0=no cases that year.

Dr. FURMAN. Although propoxyphene use has declined in recent months, propoxyphene involvement in drug related deaths is decreasing at a faster rate than the decline in propoxyphene prescriptions. In the bar graph, graph II, all prescriptions for propoxyphene have been compared with DAWN medical examiner propoxyphene mentions. Despite quarterly variations, the trend is clearly downward.

GRAPH II



*Represents all reports received by IMS America, Ltd. as of 2/29/80.

Dr. FURMAN. The DAWN system also collects information from emergency rooms. Propoxyphene mentions from DAWN emergency rooms declined 36 percent between the first quarter of 1977 and the fourth quarter of 1979. They declined 27 percent in 1979 alone.

During the proceedings last year the DEA polled drug abuse officials in all States about propoxyphene. Responses were received from only 27 States. Only five said there was any evidence of abuse; only three State officials endorsed placing propoxyphene in schedule II.

Analysis of DEA drug abuse warning network data showed that propoxyphene was rarely abused for psychic effects or dependence. There has never been any evidence of illicit traffic from legitimate channels of distribution.

Recently Lilly conducted a study of more than 2,500 patients who received propoxyphene prescriptions and who were chosen to be statistically representative of 1.8 million persons who received prescriptions under third-party drug programs administered by the

Prescription Data Services Corp. The study showed almost no evidence of persons who obtained propoxyphene in quantities greater than those needed for legitimate medical purposes. In fact, over 99 percent of the persons in the sample received only the amount of propoxyphene needed for dosages recommended in the approved labeling for the drug. In short, the leading indicators provide reassurance that the FDA and Lilly information programs have been effective in that propoxyphene misuse is steadily decreasing.

Recently, as you heard Dr. Crout say, he wrote Lilly and questioned several aspects of the propoxyphene information program. Since the receipt of that letter, Mr. Step, Mr. Davis and I have met with Dr. Crout and his staff and discussed their concerns. We assured them that the Lilly program was not a promotional campaign. The information program developed by Lilly and the FDA involved the distribution of vast quantities of letters, brochures, package literature, patient information sheets, and "Management of Overdosage" booklets. Thousands of interviews were held and physicians' awareness of the precaution is applicable to the use of propoxyphene was sharpened.

The Food and Drug Administration, as noted in Dr. Crout's letter, relied upon data from the National Detailing Audit, an IMS service, as an indicator of physician awareness. Mr. Frank Osgood, who is here with us this morning, the president of IMS, participated in the recent FDA/Lilly conference. He advised that the National Detailing Audit does not provide an appropriate data base on which to evaluate the effectiveness of the Lilly program.

A survey designed to reflect accurately physicians' increased knowledge regarding propoxyphene has been conducted by IMS and the results have been provided to FDA. In that survey 88 percent of the physicians involved indicated an awareness of the precautions applicable to prescribing propoxyphene. A summary of that survey has been provided to you as appendix 2.

In his letter to Lilly, Dr. Crout expressed concern regarding Darvon sampling. On receiving a physician's signed request, Lilly sales personnel did leave samples of Darvon products during some physician calls. Such sampling is conducted in accordance with strict company accountability rules and in compliance with Federal regulations applicable to the distribution of controlled substances. A precise examination of company records indicates that during the educational effort sampling was at one-half the level reported to the FDA by the National Detailing Audit.

Lilly sales representatives are not, as stated in the FDA letter, paid on a commission sales basis. They are not paid bonuses in relation to physicians' utilization or rejection of any specific Lilly product. They share with other employees in an annual contingent compensation plan based on overall company performance. More than 75 percent of the men and women who are Lilly sales representatives are pharmacists, and many of the remaining 25 percent have degrees in science and/or advanced degrees. All are college graduates.

Mr. Chairman, a number of events have occurred over the past year or more which have increased physicians' knowledge regarding the proper use of Darvon. The Department of Health, Education, and Welfare disseminated information in February 1979 on

Secretary Califano's decision not to remove propoxyphene from the market and his announcement of the pending evaluation of the safety, effectiveness, and abuse liability of propoxyphene.

The FDA drug bulletin, under the caption "Fatalities Due to Propoxyphene," was distributed in March 1979 to nearly a million health professionals.

Lilly proposed in April 1979 to voluntarily disseminate to patients and to health professionals, including physicians and pharmacists, information on the proper and appropriate use of propoxyphene. The elements in that information program were developed jointly by Lilly and the FDA.

Information on the content of this program is provided below and included: Revised package literature providing additional information and emphasis on proper use; a special brochure for distribution to physicians with summary warning information and revised package literature; information sheets for distribution by pharmacists and physicians directly to patients, containing information to limit improper use of Darvon and a display of the various product forms; a revised "Management of Overdosage" booklet for physicians and emergency room personnel; drug warning letters for physicians and pharmacists; prescription vial warning stickers for use by pharmacists on Darvon prescriptions; destruction of all obsolete labeling and package literature; and distribution of appropriate quantities of the foregoing items, with business reply cards to provide for reordering: (a) To more than 120,000 physicians identified by Lilly as significant prescribers of Darvon products—75,000 physicians by personal contact and the remainder by mail; (b) to an additional 45,000 physicians; (c) to 25,000 psychiatrists; and (d) to 60,000 community and hospital pharmacists.

Preparation and distribution of a film incorporating the views of three prominent psychiatrists on the identification and treatment of depressed and potentially suicidal patients: (a) Approximately 150 copies are available in various company offices throughout the country for use by health groups; (b) all medical and pharmacy schools in the United States have been provided copies.

Surveys have been conducted: (a) To determine physician awareness of the revised warnings applicable to propoxyphene; (b) to determine pharmacy use of patient information sheets.

A survey is currently in progress to determine patient's understanding of instructions for the proper use of propoxyphene.

Lilly continues to analyze DAWN medical examiner and emergency room data.

Dr. Finkle's study of medical examiner data is going forward under Lilly sponsorship.

Dr. Robert Litman, director of the Suicide Prevention Center of Los Angeles, is conducting a 1-year study of all codeine- and propoxyphene-related deaths.

Prescription Data Services information on drug use, both with respect to propoxyphene and other agents, has been, and is continuing to be, reviewed.

Reports to the company of toxicity and dependence are investigated and tabulated.

Darvon patient information sheets have been developed in Spanish and Yiddish.

Available crime laboratory information (Wisconsin) is scanned—propoxyphene reports are negligible.

Periodic reports on all of the foregoing activities are submitted to and reviewed with the Food and Drug Administration. FDA and other agencies within the Department of Health and Human Services are continuing to evaluate propoxyphene. With surveillance both by the appropriate Federal agencies and by the company, we are confident that any significant change in public health statistics related to propoxyphene will be promptly reported and acted upon.

In summary, Mr. Chairman, an extensive information program has been conducted, and physicians are aware of the precautions applicable to the use of propoxyphene. All available data indicate that propoxyphene involvement in medical examiner cases and emergency room situations has decreased and is continuing to decrease sharply. Both Lilly and the Department of Health and Human Services are monitoring this situation on a continuing basis, and Lilly is committed to programs for the safe and effective use of Darvon products.

Thank you for this opportunity, Mr. Chairman, to present our views to you and the members of your committee. We will be glad to respond to questions.

[Attachments to Dr. Furman's prepared statement follow:]

APPENDIX I

April 24, 1980

Comment by Dr. Bryan Finkle

During the past several months a study has been in progress, the intent of which is to further examine the role of propoxyphene in sudden unexplained deaths examined by medical examiners and coroners in the United States and Toronto, Canada. The study design is very similar to that which was reported in 1976 (Finkle, B. S., et al., A National Assessment of Propoxyphene in Postmortem Medicolegal Investigation, 1972-1975, J. of Forensic Sciences, 21:4, pp. 706-742, 1976) but has involved a number of additional study sites. The total number of medical examiner and coroner offices in the current survey is 27. The following statements are an interim report of the study findings, and although they will be further substantiated in detail as the study is brought to a conclusion, it is unlikely that these statements will change in substance.

1. The number of deaths involving propoxyphene has either plateaued or decreased at every site since 1976, and although this drug still ranks amongst those agents frequently detected in drug involved cases, it has been generally superseded in the past two to three years by other drugs such as the tricyclic antidepressants, particularly amytriptyline.

2. A majority of the cases involving propoxyphene are still classified as suicides, with accidents and undetermined cases following far behind.

3. The population profile of the deceased remain very much the same as that previously reported.

4. There is little evidence that the deceased constitute a major part of the drug abuse population. They do, however, represent a medical population with a propensity for multiple drug use, apparent self-medication and frequent use of alcohol.

5. Since the publication of the earlier study there has been a general improvement in the analytical schemes and assay methods used by most forensic toxicologists with respect to propoxyphene and its major metabolite detection. At almost all of the study sites either appropriate gas chromatography or gas chromatography-mass spectrometry methods are now being used. The previously reported derivative ultraviolet spectrophotometric technique has been almost entirely discarded. One inference from this information is that a higher frequency of propoxyphene and metabolite detection, and more accurate quantitation, could be expected. However, despite this the trend in propoxyphene-related fatalities has either stabilized or decreased.

6. A preliminary scan and evaluation of the several hundred cases in this study does not reveal any special toxicological significance to the metabolite, nor-propoxyphene. There are no cases in which it could be confidently stated that the metabolite was causative in the fatality, or, indeed, could be clearly demonstrated as more toxic than the parent drug in any particular case.

7. The study continues to confirm that propoxyphene when misused can be a dangerous drug. It is apparently misused with sucidial intent and most often in combination with a variety of other centrally-acting drugs, particularly alcohol, the benzodiazepines, and the tricyclic antidepressants. Multiple drug use and self-medication without medical supervision of potent centrally-acting drugs still remain the major cause of drug-related suicides and accidental deaths. It is generally in this context that propoxyphene is detected by forensic toxicologists.

APPENDIX 2

IMS Research Group Survey of Physician Perceptions of Precautions When Prescribing Darvon

This survey was conducted by contacting approximately 460 physicians by telephone who were randomly selected from three physician lists, i.e., an IMS National Detailing Audit panel, a Lilly list of frequently detailed physicians, and a Lilly list of infrequently detailed physicians. These physicians were interviewed by telephone concerning their awareness (unaided recall) of precautions when prescribing Darvon. As a point for comparison, physicians were also surveyed to determine their awareness of precautions associated with clofibrate (ATROMID-S, Ayerst).

Among the 460 physicians surveyed, 88% indicated an awareness of precautions when prescribing Darvon. Of those indicating an awareness of such precautions, 84% cited single and/or multiple warnings associated with the misuse of the drug. These warnings included: 1) Caution when taken with alcohol, CNS depressants, or by patients who are emotionally disturbed or depressed; and 2) that Darvon may be addicting; therefore caution should be used in potential or suspected drug abusers, to avoid overdosage, to limit the number of refills, to avoid large prescription sizes, and to take Darvon only as directed. In 16% of the physicians responding, other precautions were noted. For example, caution should be used when operating machinery, when combining Darvon with muscle relaxants, or when Darvon is given to pregnant women. This 16% also includes those

physicians who did not recall specific precautions.

When clofibrate (ATROMID-S) awareness was tested with physicians, only 26% of the physicians were aware of the precautions associated with this drug.

Physicians identified a variety of sources that provided information of Darvon precautions. These physicians generally mentioned more than one source for this information. The most frequently cited sources were 1) the manufacturer, e.g. sales representatives, company mailings, journal ads. 2) Literature, e.g. magazine articles, MEDICAL LETTER, periodicals, and 3) other sources, e.g. Physician Desk Reference (P.D.R.), newspapers, television.

Mr. WAXMAN. Thank you, very much, Dr. Furman, for your statement.

You have patient information sheets in Spanish and Yiddish. Spanish, of course, is probably the most widely used second language in this country. Why Yiddish?

Dr. FURMAN. You will have to ask some of my marketing friends for that answer.

Mr. WAXMAN. Are they here with you today?

Dr. FURMAN. Mr. Step, who knows all the answers, can answer that. We will be happy to find that out.

[The following information was received for the record:]

Our long experience in providing information to diabetics in conjunction with insulin therapy has indicated that there are significant constituencies, i.e., population groups, who benefit from the availability of this information in their own language. Consequently, Lilly, on its one initiative, arranged for the translation and preparation of materials in the languages noted.

Mr. WAXMAN. One alternative to rescheduling would be to have physicians write on the prescription "do not refill." This would give the physician the ability to check to be sure that the patient is not abusing Darvon. Do you think that it would be a good idea for physicians to write "do not refill" on Darvon prescriptions?

Dr. FURMAN. In certain cases I certainly do and that is recommended by the psychiatrists in our film. If a patient is known to be

one who has attempted suicide in the past, obviously refillability should be limited. The psychiatrists in the film also suggest that a member of the family be advised of the prescription, what it contains and what it is for, in order to have a sort of a built-in monitor. I think, however, rather than to insist on imposing a regulation, physicians should make this decision and I think they are increasingly making this decision.

Mr. WAXMAN. If Darvon were reclassified into schedule II, one of the major differences would be that physicians would be required to review each prescription. Since there is so much Darvon abuse, would it not be a mild inconvenience to have physicians regularly review the prescription before renewing it as opposed to allowing refills five times within 6 months without physician review?

Dr. FURMAN. First, 60 to 80 percent of the deaths in association with Darvon are suicides. Furthermore, there are upward of 30 to 50 million people in the United States who suffer from chronic pain disorders, various forms of arthritis and rheumatism. To arbitrarily impose on these disabled patients, in many instances, the requirement and the expense and time required to go back to the physician and have a new prescription written, I think imposes an unnecessary burden both on the patient and the physician. I think the answer to the problem is not the arbitrary imposition of these kinds of restrictions but to increasingly make the physician aware of this kind of thing when he perceives in his patient the potential for abuse.

Mr. WAXMAN. Do you believe the abuse of Darvon is in any way related to the ability of patients to obtain refills without a physician's supervision?

Dr. FURMAN. I cannot say that it is not. To the extent that it is, I would hesitate to say. Perhaps Dr. Scherbel could comment on that.

Mr. WAXMAN. I would prefer to do this, if I might. We are going to have to respond to a vote on the floor. If there is additional material you think would be helpful to us, I will keep the record open to receive this information.

Dr. FURMAN. Thank you. I am sure there is.

[The following information was received for the record.]

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EIGHTY-SECOND ANNUAL MEETING: NEW ORLEANS, LOUISIANA — MARCH 19-20, 1981
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June 9, 1980

The Honorable Henry A. Waxman
Chairman, Subcommittee on Health
and the Environment
Committee on Interstate and Foreign Commerce
U.S. House of Representatives
2415 Rayburn House Office Building
Washington, D.C. 20515

Re: Hearing on Darvon

Dear Congressman Waxman:

During the hearing on May 21, you asked Dr. Furman if it is possible that the abuse of propoxyphene is in any way related to the ability of patients to obtain refills of prescriptions. Dr. Furman suggested that I might respond, and you indicated that you would receive comments from me for the record. I am pleased, therefore, to submit the following observations with respect to your question.

During the last 25 years as Chairman of the Department of Rheumatology, which I founded at the Cleveland Clinic, I have had a deep interest in clinical pharmacology and the development of new agents for the treatment of disease. In addition, I have recently served as President of the American Society For Clinical Pharmacology and Therapeutics.

During the course of my practice, I have had the opportunity to treat large numbers of patients with various types of arthritis as well as patients with other painful conditions. Consequently, I have had extensive experience in the use of a variety of analgesic agents and am well aware of their relative safety and efficacy.

AMERICAN SOCIETY FOR
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SEVENTY-NINTH ANNUAL MEETING: ATLANTA, GEORGIA — MARCH 29-31, 1979
HEADQUARTERS: PEACHTREE PLAZA HOTEL

In over 20 years of propoxyphene prescribing at the Cleveland Clinic, I have not found this drug to be addictive in any of the patients that I have treated. Because pain associated with arthritis is often chronic in nature, refill of prescriptions is often permitted patients on relatively long-term therapy. However, as noted above, I have never found this drug to be addictive. Rarely have I observed a dependency reaction with respect to the drug. However, susceptible patients may become dependent on many common items that are used daily without prescription, such as coffee, nicotine, alcohol, food and even sugar. Any experience associated with improvement in the feeling of well-being may engender some form of psychological dependency.

I have reviewed the possibility of propoxyphene toxicity and dependence with appropriate staff personnel at the Cleveland Clinic and Cleveland Clinic Hospital. During the past year, 364,000 patients were seen at these institutions. No patients seen in the Clinic were subsequently admitted to the hospital because of propoxyphene addiction. No patients seen in the emergency room were admitted to the hospital because of propoxyphene toxicity or death-related overdose. The Chairman of the Psychiatry Department and the Head of the Section of Pain Management are in agreement with these statements, and the Chairman of the Department of Pharmacology informs me that he is not aware of patients coming to our emergency room because of propoxyphene abuse or intent to commit suicide with the use of propoxyphene. He also advises me that treatment with propoxyphene has not been a problem in patients with continued pain.

Consequently, I do not believe that permitting the refill of propoxyphene prescriptions within the limitations imposed by Schedule IV of the Controlled Substances Act is a factor in the misuse of the drug. In this regard I have discussed propoxyphene with personnel at the Cleveland Drug Center who are involved in the treatment of drug abusers. They inform me that propoxyphene is not a popular street drug. In their experience, propoxyphene is used only by those addicts when they are unable to obtain a more potent drug at a particular time of need.

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CLINICAL PHARMACOLOGY AND THERAPEUTICS

ORGANIZED MAY 1, 1900
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One other observation may be of interest. Physicians have available only a limited number of drugs which are effective in the management of pain. Several of these were mentioned during the hearing. Drugs such as aspirin and acetaminophen also afford pain relief but each has significant side-effects and toxicity. Aspirin causes irritation and erosion of tissue in the stomach and upper gastrointestinal tract. Acetaminophen may produce significant liver toxicity. Codeine frequently causes constipation and may be addictive. Oxycodone, pentazocine and various other drugs can also cause dependence as well as chronic irritation. None of these agents is free from disadvantageous characteristics. All, including propoxyphene, should be reasonably available for the care of patients by well-informed and responsible physicians.

I hope this letter has been helpful. In my view, propoxyphene should remain available as a Schedule IV agent. In my judgment further restrictions on its availability would be a mistake and would only serve to make the practice of medicine more cumbersome for the physician and increasingly frustrating to the patient.

Thank you for your courtesy and kind consideration in reviewing these comments and providing for their placement in the record of this hearing.

Sincerely yours,

Arthur L. Scherbel, M.D.

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Mr. WAXMAN. In Dr. Crout's March 17, 1980, letter he wrote that for Eli Lilly's informational campaign to be meaningful the intent of every visit by sales representatives must be "to emphasize the precautions necessary for the judicious prescribing and safe use of these products." He went on to add that this message should be conveyed unencumbered by any diluting or qualifying information, in 100 percent of the visits made.

Has Lilly's informational campaign adhered to this standard?

Dr. FURMAN. Well, I think that is a highly idealized situation and I dare say Dr. Crout, on reflecting, might agree. The sales representative is allowed an opportunity to discuss matters with the physician at the pleasure of the physician. The physician is a busy man and if he feels that he is sufficiently aware of the proper prescribing and use of propoxyphene, he is not going to allow a detail man to occupy the 5 or 10 minutes which would otherwise be required for such communication and will insist on talking about something else and in an area where he is not so well informed. So I think it is really unrealistic to expect an interview to be limited solely to Darvon, its precautions and uses, when the physician says, "Look, Mr. Lilly, I am well aware of those things, I want to talk about something else."

Mr. WAXMAN. Do you agree that part of the Darvon problem has been the physicians' ignorance of the dangers posed by its abuse and the fact that in the past the information they received through the merchandising techniques in the company has been deficient in giving that information to them?

Dr. FURMAN. I would not agree that it is deficiency in merchandising techniques. I think you have to realize that this drug has been available for more than 20 years. Literally billions of doses have been administered. It is highly useful for physicians who have practices such as Dr. Scherbel. I think there has grown a tremendous experience on the efficacy of Darvon and the practice of the physician has been thoroughly established by this past satisfactory performance.

Mr. WAXMAN. We have heard testimony that perhaps 20 years ago many thought that Darvon was a perfectly safe, nonnarcotic analgesic and was represented as such to physicians. More recently we have learned Darvon is a narcotic and that its abuse poses very serious dangers.

Dr. FURMAN. Anything that has been said about the propoxyphene products must, of course, conform to FDA approved labeling. The idea that it was nonnarcotic arose understandably enough from the decision of the WHO–U.N. apparatus that it did not need to be classified in the U.N. convention schedule II. The studies in subhuman primates and in humans, as well as in animals, indicated that the dependence liability of propoxyphene was not only substantially less than that of morphine but less than that of codeine and as the years went by after the propoxyphene products were introduced to the market by Lilly—and there is certainly a period for many years of no evidence of any dependence liability or any dependence creation—the notion gained acceptance that this was a safe drug, that it had very little, if any, dependence liability and the fact that it was a narcotic was more or less a legal issue.

Now we have heard this morning several times that it is closely related to methadone. Chemically it is. But estrone and testosterone account for much of the difference between men and women and differ chemically very little. If you take propoxyphene and take the levorotatory form rather than the dextrorotatory form, chemically identical, the levorotatory form has no dependence liability potential and is not analgesic.

Mr. WAXMAN. We have to respond to a vote on the floor. We will recess for such time as it will take us to get to the floor and come right back.

Dr. FURMAN. Thank you.

[Brief recess.]

Mr. WAXMAN. Dr. Furman, your interpretation of the recent U.N. action is that it has no regulatory impact on the United States. Is that correct?

Dr. FURMAN. That is correct.

Mr. WAXMAN. What was the U.S. vote on that issue in the U.N.?

Dr. FURMAN. Affirmative.

Mr. WAXMAN. For the placement of propoxyphene in schedule II?

Dr. FURMAN. Yes.

Mr. WAXMAN. Article 21 of the 1961 Singles Convention on Narcotic Drugs states that, The total of the quantities of each drug manufactured and imported by any country or territory in any 1 year shall not exceed the sum of the following," and it lists five items. Have you had an opportunity for your lawyers to review article 21 and assess its impact?

Dr. FURMAN. May I ask my colleague Mr. Davis to respond to that?

Mr. WAXMAN. Yes.

Mr. DAVIS. Thank you, Mr. Chairman.

Yes, we have asked most international legal experts, including the former legal advisor to the State Department under Secretary Vance, and we have also spoken with the senior officials of the United Nations Commission on Narcotic Drugs and the International Narcotic Control Board with respect to the question you asked. The essential answer is that the intention of the treaty is to put production curbs on any illicit manufacture of a drug but not to restrict the production of a drug for legitimate medical use under prescription or any other legitimate dispensing by the physician. Since it is well known that in the United States there is no illicit manufacture of consequence, the opinion of counsel is that it is quite possible for the Government to comply administratively with the requirements of the treaty by simply providing the United Nations with the annual reports of total production of propoxyphene since all of it is for legitimate medical use in the United States.

In fact, just very briefly, conversations with those senior officials of the United Nations has indicated that the Single Convention does not mandate or impose any particular method of control within a given country nor is it intended to curb drug production for legitimate uses. Its purpose is to assure that the production and distribution of scheduled drugs correspond generally to the amounts required by physicians and for other legitimate medicinal uses. So with respect to dextro-propoxyphene the U.N. officials

observed that it is a well-known fact that it is not a drug of significant diversion or illicit manufacturer and that there is no intention in the U.N. action to curb production which is being used to fulfill legitimate medical needs. Therefore, it is quite possible for the United States to comply with the requirements of the treaty without having to impose production curbs on legitimate production.

Mr. WAXMAN. Mr. Leland.

Mr. LELAND. Thank you, Mr. Chairman.

Dr. Furman, you were saying that 75 percent of your detailed personnel were registered pharmacists; is that correct?

Dr. FURMAN. Yes, sir.

Mr. LELAND. And 25 percent or the large portion of your other sales, your detailed personnel, were science oriented people, people who had backgrounds in science?

Dr. FURMAN. That is correct, Mr. Leland.

Mr. LELAND. You stated also in light of that that the detailed personnel have not really had the opportunity to communicate with the doctors specifically to any great length about the adversities of Darvon, the question of dangers of Darvon.

Dr. FURMAN. If I said that, I didn't mean to say that.

Mr. LELAND. If you will clear that up?

Dr. FURMAN. The sales representative, the detailman, sees the physician at the pleasure of the physician. If he begins a discourse which the physician feels is redundant and is not telling him anything he does not know, he is going to say, all right, Mr. Lilly or Mr. Leland or whoever it happens to be, I am aware of those things, there are some things I would like to know. He is the one that controls what is discussed, within reason.

What I am saying is that when Dr. Crout suggested or requested that the sole purpose of the visit be to detail the physician on the proper use and hazards of propoxyphene that this is not always something that can be accomplished because a large number of physicians are abundantly aware of the precautions that must be exercised for the use of propoxyphene as a result of great coverage of the propoxyphene problem by various media, including the FDA publications and our own efforts. So I think it is an unrealistic goal, although theoretically an ideal one. It is unrealistic to expect that a physician is going to sit still for a discourse with which he is already familiar. That is what I had in mind.

Mr. LELAND. However small or great that discourse is, do your detail personnel ask the physicians to exercise their right to write on this prescription "do not refill?"

Dr. FURMAN. I can't speak to that precisely. So many prescription blanks have a place for the physician to indicate no refills or one or so many so that option has always been available to the physician.

Mr. LELAND. But I mean in terms of the danger that we have discovered to be prominent surrounding Darvon—you are saying that you really don't encourage the doctors to use that particular phrase.

Dr. FURMAN. I think it would be a bit presumptuous of us, Mr. Leland, because I think that is a decision the physician has to make, based on the patient, whether the patient has a psychiatric

history, whether the patient has abused drugs in the past, whether there is any history of suicidal attempts. On the other hand, the average patients that Dr. Scherbel sees who are accustomed to using Darvon and other analgesics, such a restriction would be undesirable so I think it is a matter of the physician's judgment.

Mr. LELAND. The doctor you refer to is obviously very prominent and has limited more attention to this matter than probably the average physician. I realize that you are using him possibly as an example of the American doctor or a physician who uses this product, but what about the dangers to the people in your whole educational program? More often than not the doctors need the encouragement and advice of people who know more about the drug's usage and the drugs themselves. Doctors are not that well versed in pharmacology and in a lot of instances pharmacists are much more able to do this.

As I understand it, the physicians in medical school learn something like—1 year they take a course or in some places a semester of pharmacology whereas the pharmacists, 75 percent of your detail personnel, have gone to school 5 years and 3 years spent in that and related subjects. Do you not feel that your sales task force or your detail personnel would be more adequate in delivering that kind of information?

What I am saying is in my opinion I don't think it is a presumption on your part. I think it is an obligation that you have.

Dr. FURMAN. Well, to the extent that the physician and pharmacist should be trained to assure the proper prescription and use of propoxyphene or any other drug, I could not agree with you more, I think you are exactly right. We have always felt that the physician and the pharmacist should act as a team. When it comes, however, to a decision regarding the appropriateness of a drug for a given patient, I think that is a decision that is quite apart from knowledge of the pharmacology or the metabolism of the drug. Now granted the physician can prescribe and use the drug much more intelligently and appropriately if he is aware of the kind of information that our sales people and pharmacy trained people can provide him, but the decision as to whether to use the drug, how much to give, what dosage and to what extent it can be refilled is more a clinical judgment than a pharmacologic one.

Mr. LELAND. Of course, but the problems we are realizing today, it seems to me that an encouragement on the part of the detail person should be exercised in order that we can somewhat limit the problems that we are having, particularly in light for lobbying in my estimation against changing the schedule. Am I presumptious to say that you are——

Dr. FURMAN. No.

Mr. LELAND. It just seems to me that should be the case and I am not discouraging discourse on that point.

Let me ask you one other thing which it probably will be considered terribly crass of me because we have been talking about the therapeutic value and the importance of the health of human beings but let me ask you what would be the economic impact of rescheduling Darvon from schedule IV to schedule II?

Dr. FURMAN. Well, I cannot answer that with any precision. I think it is a foregone conclusion that the number of prescriptions

written would go down that it would be incumbent upon the patients to return to the physician for a visit for renewal and, as I said before and as Dr. Scherbel has pointed out in his testimony last year, this imposes a really cumbersome and unnecessary burden on that vast majority of patients who use the drug properly and effectively.

Mr. LELAND. Dr. Furman, it is our responsibility to look after the safety and welfare of the people of our country by way of legislation and the responsibilities imposed on us by our elections and our service in this Congress. It seems to me that when you deal with priorities that the saving of one life, the lessening of ill health proposed by abuse of drugs or otherwise is a whole lot more important to the American people than imposing an economic burden on the people. Would you not agree with that?

Dr. FURMAN. I agree with that. I think we both have the same end in mind but are embracing different approaches to the accomplishment of that end. I think the way to handle the problem is to bring physician awareness and knowledge to a point where this problem is, in essence, solved not by imposing an arbitrary restriction on his use of the drug because we cannot legislate morality, we cannot eliminate suicide in this country by banning a drug at one time or another that happens to be a very popular item for suicide. Suicide is a psychiatric societal problem whether we are talking about the use of a Saturday night special or a car in a garage with a motor running and the door down or amitriptyline or propoxyphene or codeine or what have you. I don't think the way to get the solution to this problem is by imposing restriction on the number of refills.

Mr. LELAND. Do you think we ought to legalize cocaine?

Dr. FURMAN. Why are you asking that?

Mr. LELAND. I ask you that because if cocaine was allowed to be accessible to the general public, then the abuse of cocaine would not necessarily be restricted.

Well, let me put it another way. I am trying to bring a parallel with what your example was. If we make Darvon more restrictive, it is not going to decrease the incidence of suicide which is the conclusion I draw from you.

Dr. FURMAN. I think it would decrease a little. I think it would have a negligible impact on the suicide rate. It would decrease the number of suicides from Darvon but it would not decrease the suicide number in the United States, they would move to another drug, they already are.

Mr. LELAND. Is that what you are saying?

Dr. FURMAN. All the evidence indicates that. Amitryptyline has displaced propoxyphene in the list of prescription drugs of abuse and the number of medical examination cases involving amitryptyline is going up sharply, while the number for Darvon is going down.

Mr. LELAND. Then maybe we should further restrict that drug.

Dr. FURMAN. At the moment——

Mr. LELAND. Let me ask you one final question because I understand what you are saying.

I am truly concerned about this. I learned as a pharmacist that all drugs were potential poisons and that drugs were merely substi-

tutes for lack of the kinds of substances in our bodies that were necessary in order to affect the health of the person and that when we can avoid using drugs we should as much as possible, whether that is by restriction in law or policy or by the total elimination of the production of those drugs altogether. I realize that in a free enterprise system we have to exercise some kind of concern about the competitiveness in terms of Darvon as opposed to some other drug, aspirin or otherwise, in terms of trying to avail the public of means to a healthy body. However, we have determined that in contemporary times that the increasing problem of drug abuse and drug usage, we are going to have to do something—something that is significant and probably something that is much different than what we are used to, even violating sometimes the integrity of the free enterprise system.

If, in fact, you had determined that Darvon is tremendously dangerous to the public, would you be willing to advise your company to take Darvon off the market? Without provocation on the part of the FDA?

Dr. FURMAN. If it suddenly should become evident that people were dying suddenly, for an heretofore unknown reason but a reason now known to be due to some effect of Darvon or propoxyphene, the Lilly Co. would say this is a dangerous drug and it should be controlled. But that is not the situation with Darvon.

Mr. LELAND. I won't go into that.

Dr. FURMAN. I am entirely in sympathy with your aims and I would hope that you and I and other members of this committee might after this session, at some convenient time, continue this dialog because I think you are touching upon a terribly important aspect of a societal problem.

Mr. LELAND. I am just reminded of my attempt to try to ban the sale of amphetamines in Texas. Amphetamines have no real therapeutic use but hurt a lot of people. Your organization, the Pharmaceutical Manufacturers Association, all came down to Austin, Tex., and they whipped my behind quite frankly. You just banned together and overwhelmed me with your political influence and no one could say that amphetamines served any real therapeutic purpose. Some psychiatrists say we ought to reserve the right of psychiatrists to use amphetamines in some extreme instances but in terms of the prominence of the sale of amphetamines on the market that was unjustifiable and that is not just my opinion, it was the opinion of the law enforcement officers, the opinion of pharmacists, the opinion, off the record, of one or two of the manufacturing company representatives.

Mr. WAXMAN. Would the gentleman yield?

Mr. LELAND. I will.

Mr. WAXMAN. I think we have to be concluding the hearing shortly but I would like to respond to the statement just made by the gentlemen from Texas regarding his personal experience, I would not want him to engage in stereotyping all people in industry or all companies in the industry. I would be the first one to feel that stereotyping would be an unfair way to treat people.

Mr. LELAND. I yield to the wisdom of my chairman and the only reason I had an iota of stereotyping was because I was amazed at

the information specification that they were using the translation of Spanish and Yiddish.

Mr. WAXMAN. I won't comment on that.

Mr. LELAND. I am just trying to figure out whether or not the Jewish community in this country are inclined more to the abuse of Darvon than anybody else.

Mr. WAXMAN. We are both interested in that question.

What we have here, unlike what Mr. Leland maintains for amphetamines, is a drug which is regarded to have a legitimate therapeutic purpose. I have not heard that disputed but I hear from everyone concerned that this is a drug that when abused is extremely dangerous. How best we can limit the abuse of that drug is a question that we have to think through together. As I understand what you are saying, Dr. Furman, it is that you think the limiting of that abuse can best be brought about through an educational campaign by informing physicians that there are dangers with certain kinds of patients who are likely to abuse it and they have to be aware of that fact.

Dr. FURMAN. And the patients, too, Mr. Chairman.

Mr. WAXMAN. And the patients, too.

Another approach would be placing the drugs in a more restrictive schedule. I am wondering however, whether rescheduling is a substitute for education of the physician and the patient. It seems to me that without the educational campaign even rescheduling would not accomplish the results that all of us would like to see in reducing abuse of the drug.

Dr. FURMAN. I cannot help but agree that the informational and educational aspects of what you are saying represent the way to get the job done. To me placing these arbitrary restrictions on the availability of the drug will not address the basic problem of drug abuse and suicide with drugs in the United States.

Mr. WAXMAN. On the other hand, a rescheduling which would make the drug less available would by its nature mean that it would be less subject to abuse.

Dr. FURMAN. Is there any advantage that if the Saturday night special is used the use of propoxyphene is sharply curtailed?

Mr. WAXMAN. I think our concern ought to be not for those who are intentionally out to commit suicide, whether they use propoxyphene or Darvon or the Saturday night special or some other method to accomplished the suicidal intent. It is still something beyond our control but I think we ought to be concerned about those who are not aware who will be using the drug thinking that it is not going to do them the type of harm.

I am trying to figure out a summary of where we are. I think the summary is that we all share the basic goal of trying to protect the abuse of this drug and after this examination we will have to look to see if there is any legislative role for us to play, and whether there is or not this was a use of our oversight role here from the FDA, the Health Research Group which has taken such an active part in addressing the concerns about this one drug and those of you who represent the industry. I think it has been very helpful to us who have your testimony and for you to be with us today.

We will leave the record open to receive any additional information that we did not have included through this morning's hearing.

Dr. FURMAN. Thank you, Mr. Chairman. I would just like to leave with the hope that something is working. The death rates and abuse are plummeting and I would hope that we would maintain a posture of careful scrutiny and watchful waiting to see what the ensuing months bring in the way of accomplishment of our goals which we share mutually.

Thank you very much.

[The following material was received for the record:]

ELI LILLY AND COMPANY
June 3, 1980

MEMORANDUM

Abuse Potential and Dependence
Liability of Propoxyphene

This memorandum summarizes information concerning the potential for abuse and dependence liability of propoxyphene, placing special emphasis on information that has been developed since those questions were considered by the Food and Drug Administration's Drug Abuse Advisory Committee last year. The memorandum discusses a recently completed review of scientific studies of the dependence liability of propoxyphene; a report on the most recent study of propoxyphene-related fatalities by Dr. Bryan Finkle, of the University of Utah; a response to certain allegations concerning propoxyphene abuse made in a hearing before the Subcommittee on Health and the Environment of the House Interstate and Foreign Commerce Committee on May 21, 1980; and an interim report by Dr. Robert E. Litman on a comparative study of propoxyphene and codeine overdose deaths in Los Angeles.

The abuse potential and dependence liability of propoxyphene were considered in detail in the proceedings before FDA's Drug Abuse Advisory Committee last year. As the summary presented in this memorandum shows, there have been no developments since

then that warrant any change in the Committee's recommendation that propoxyphene should remain in Schedule IV under the Controlled Substances Act. In particular, it is clear that propoxyphene does not possess the "high potential for abuse" or the potential for producing "severe psychological or physical dependence" that are required for classification in Schedule II under the Act.

Potential for Abuse

Numerous general investigations of drug abuse conducted over the past twenty years, as well as inquiries directed particularly at propoxyphene, have revealed no significant problem of "street abuse" of the drug. Congressional hearings in the mid- and late 1960s on the Drug Abuse Control Amendments to the Federal Food, Drug, and Cosmetic Act and on the Controlled Substances Act, hearings in the late 1960s and early 1970s before the House Select Committee on Crime, and investigations by the National Commission on Marihuana and Drug Abuse all failed to disclose any problem of propoxyphene abuse. When FDA's Controlled Substances Advisory Committee recommended in 1976 that propoxyphene be placed in Schedule IV under the Controlled Substances Act, it did so not on the basis of evidence of "street abuse" but on the basis of evidence from a

Lilly-sponsored study conducted by Dr. Finkle which showed that propoxyphene had been misused (frequently in combination with alcohol or other drugs), most often for suicidal purposes.

Propoxyphene's limited potential for abuse was reconfirmed in proceedings before FDA last year. Eminent physicians who use propoxyphene in a variety of clinical settings stated that their patients did not abuse the drug. The Drug Enforcement Administration's survey of state drug abuse enforcement officials showed that there was little "street abuse" of propoxyphene and that there was virtually no support among state officials for stricter control over the drug.

In its quarterly reports on propoxyphene, Lilly has informed FDA of a study being conducted by Dr. Robert E. Litman, codirector of the Institute for Studies of Destructive Behaviors and the Suicide Prevention Center in Los Angeles, to compare the psychological characteristics of persons who died of overdoses of propoxyphene and codeine. An interim report, recently received from Dr. Litman, states, among other things, that codeine-related deaths were more likely to involve drug addiction and illegal drug use while propoxyphene overdose deaths more commonly involved mentally disturbed persons whose motivations appear to be suicidal and who obtained the drug through legitimate prescriptions. According to Dr. Litman, the number of codeine-

related deaths in Los Angeles is about twice the number involving propoxyphene.

In the recent House Subcommittee hearing on propoxyphene, Dr. Sidney Wolfe, of the Health Research Group, suggested, contrary to the evidence in all prior proceedings, that propoxyphene has been subject to significant "street abuse." His contentions are reviewed in detail in Attachment 1 and are shown to be based on insubstantial evidence or misleading characterizations of data.

The only significant development since last year's proceedings has been a steady and substantial decline in the incidence of reports of propoxyphene misuse. In its testimony to the House Subcommittee on May 21, Lilly noted that the number of medical examiner reports to the Drug Abuse Warning Network that mention propoxyphene had declined by 55% since the first quarter of 1977, including a decline of 30% since the spring of 1979. There have also been similar declines in emergency room reports to the DAWN system that mention propoxyphene. Recently, Dr. Bryan Finkle, director of the Institute for Human Toxicology at the University of Utah, completed a new survey of medical examiner offices in localities throughout the United States and Canada that confirms the downward trend in propoxyphene-related fatalities. A summary of his report is enclosed as Attachment 2.

Dependence Liability

Evidence presented in the proceedings last year clearly showed that propoxyphene does not have the capacity to induce severe psychological or physical dependence. Laboratory and clinical studies, including studies conducted by the U.S. Public Health Service Addiction Research Center, have shown that propoxyphene's dependence liability is a small fraction of that of morphine and substantially less than that of codeine.

In the more than twenty years since propoxyphene was introduced into the market, Lilly has received only 440 reports of alleged dependence on the drug. About 155 of these reports provided sufficient information to support an inference of dependence (55 involved physical dependence; and 100, psychological). No form of dependence has occurred at recommended doses. As several witnesses testified in the proceedings last year, propoxyphene has been used in millions of patients for the long-term treatment of chronic conditions (such as the pain of arthritis) without producing dependence. Only 5.4% of the emergency room reports in DAWN VI that mention propoxyphene attribute its misuse to dependence.

A new review recently completed by Lilly confirms the conclusion reached by the Drug Abuse Advisory Committee that

propoxyphene does not have the capacity to produce severe dependence. Lilly examined reports of pharmacological investigations of propoxyphene's ability to produce physical dependence, as measured by standard tests, and its capacity to produce psychological dependence, as measured by euphorigenic properties and inducement of drug-seeking behavior. The review shows that propoxyphene's dependence liability is much less than that of morphine, comparable to that of pentazocine, and less than that of butorphanol and nalbuphine. Pentazocine is a Schedule IV analgesic. Nalbuphine and butorphanol are not currently in any schedule under the Controlled Substances Act, but FDA has recommended that they be placed in Schedule V. The review also shows that propoxyphene's capacity to induce psychological dependence is significantly less than that of the amphetamines and sedative-hypnotics in Schedule II.

Another study recently completed by Lilly provides additional evidence that drug dependence and "street abuse" are not significant problems with propoxyphene. This survey covered more than 2,500 patients who received propoxyphene prescriptions and who were chosen to be statistically representative of 1.0 million persons who received prescriptions under third-party drug programs administered by Prescription Data Services Corporation. The study showed almost no evidence of persons who

obtained propoxyphene in excessive quantities. Even though persons who participate in third-party drug programs have an economic incentive to obtain excessive quantities of drugs, 99.5% of the persons in the sample received no more propoxyphene than was needed for dosages recommended in the approved labeling for the drug.

Conclusion

Propoxyphene has not been shown to possess the severe dependence liability or the high potential for abuse that characterize the drugs currently in Schedule II of the Controlled Substances Act. Extensive studies and long clinical experience have shown it to be a useful analgesic that does not possess a number of the disadvantages of other widely accepted pain-relieving drugs.

FDA's Drug Abuse Advisory Committee was aware of these facts when it concluded that an information program directed to physicians, pharmacists, and patients would be more effective than Schedule II controls in dealing with propoxyphene misuse. As FDA recognized in its statement to the House Subcommittee on May 21, the agency accepted the Advisory Committee's recommendation because it was felt to address most directly the major

problem associated with propoxyphene misuse, and because rescheduling was not the appropriate remedy for the problem of overdose deaths.

Experience has shown that the Advisory Committee's recommendation was correct. The dramatic decline in propoxyphene-related deaths since the first quarter of 1977 must be attributed in part to the educational efforts undertaken by Lilly and FDA in 1976. The greatly expanded programs initiated by Lilly and FDA last year have contributed to the further decline since the spring of 1979.

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Eli Lilly and Company
June 3, 1980

MEMORANDUM

ADDITIONAL COMMENTS

The following memorandum presents additional information on a number of points raised during the hearing concerning the safety of propoxyphene held by the House Subcommittee on Health and the Environment on May 21, 1980. This information is provided in response to Chairman Waxman's invitation to elaborate on aspects of the testimony which would be helpful to the Committee.

1. No correlation between amount of propoxyphene prescribed and the amount abused. There is not a "close correlation between the amount of propoxyphene prescribed and the amount abused." As shown in the Lilly testimony of May 21 [1], there has been a statistically significant decline in the number of DAWN medical examiner (DAWN-ME) mentions of propoxyphene per 1000 new prescriptions. The same is true for DAWN emergency room (DAWN-ER) reports. Table 1, attached, presents this data for the period 1976(Q1) through 1979(Q4). These data confirm propoxyphene misuse is decreasing even more rapidly than prescription volume.

When comparing reports of misuse of a drug over time, DAWN's sponsors clearly state that "consistently reporting" MEs and ERs reports must be used. Otherwise, fluctuations (up or down) could be due to a larger or smaller number of reporters rather than reports. NIDA carefully adheres to this consistent reporter convention in their published DAWN Quarterly Reports of time trends in drug abuse/misuse. The Health Research Group did not uniformly and appropriately employ consistently reporting DAWN-MEs and ERs in its testimony, thus weakening the analytical support for its conclusions.

2. Reliable data from the DAWN reporting system are available for analytical purposes for the year 1979. 1978 is not the last year for which "complete death data" are available from DAWN. DAWN-ME records provide both the date of death and the date the incident is reported to DAWN. From an analysis of the reporting "lags" in past DAWN-ME cases it is possible to quantify the system's reporting patterns. These are summarized in Chart 1, attached.

Table 1

PROPOXYPHENE:
MEDICAL EXAMINER MENTIONS PER 1000 NEW PRESCRIPTIONS,
EMERGENCY ROOM MENTIONS PER 1000 NEW PRESCRIPTIONS,
PROJECT DAWN CONSISTENT REPORTERS, 1976-1979.

Time Period	# New Rxs (000)	ER Mentions	# ER Mentions / 1,000 New Rx	# ME Mentions	# ME Mentions / 1,000 New Rx
1976					
Q1	4,387a	908	.207	125	.028
Q2	4,387a	947	.216	130	.030
Q3	4,387a	1,000	.228	112	.026
Q4	4,387a	1,002	.228	129	.029
Total 1976	17,548	3,857	.220	496	.028
1977					
Q1	4,297	932	.217	162	.038
Q2	4,818	952	.198	140	.029
Q3	4,366	874	.200	145	.033
Q4	4,465	883	.198	116	.026
Total 1977	17,946	3,641	.203	563	.031
1978					
Q1	4,558	859	.188	128	.028
Q2	4,303	780	.181	102	.024
Q3	4,351	839	.193	112	.026
Q4	4,315	763	.177	92	.021
Total 1978	17,527	3,241	.185	434	.025
1979					
Q1	3,749	822	.219	105	.028
Q2	3,601	649	.180	89	.025
Q3	3,358	653	.194	73	.022
Q4	3,328	599	.180	52b	.016b
Total 1979	13,936	2,723	.195	319	.023

Notes:
a: Average by quarter; year-total from IMS audits.
b: All reports received through 2/29/80 by IMS America Ltd.

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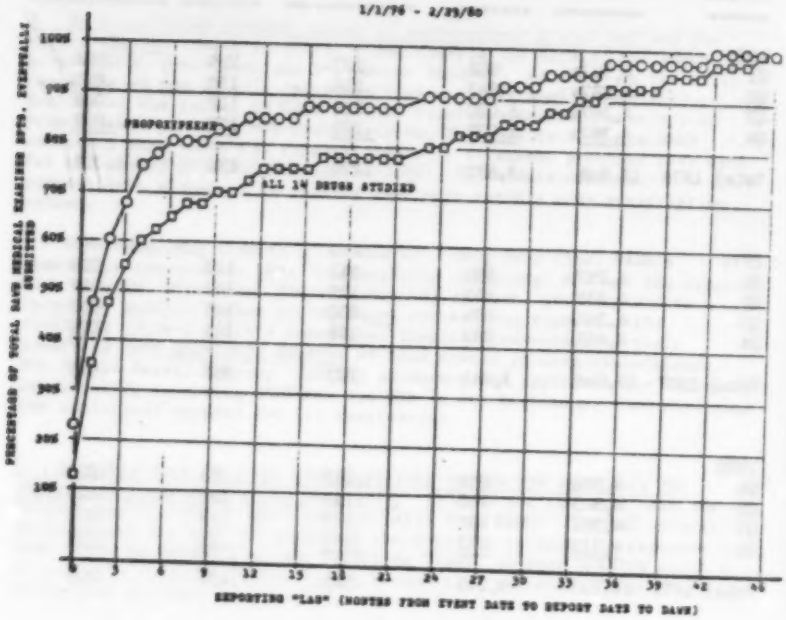
CHART 1

ANALYSIS OF REPORTING "LAG" OF MEDICAL EXAMINERS TO DAWN

ACCUMULATIVE PERCENTAGE OF REPORTS EVENTUALLY RECEIVED VERSUS MONTHS OF "LAG"

CONTRASTING PROPOXIPHENE WITH ALL DRUGS STUDIED

1/1/76 - 2/29/80



For example, based on these historical patterns, DAWN-ME propoxyphene reports for September, 1979, were nearly 80 percent complete by the end of February, 1980. Reports for the months earlier in 1979 approach 90 percent completion. The last 10 percent of DAWN-ME reports are characteristically slow in arriving -- to the extent that even 1976 and 1977 data still have a finite probability of being revised. The first three quarters of 1979 DAWN-ME data can reasonably be used in trend analyses if one understands and allows for these ME reporting patterns. Lilly staff obtained DAWN master files, complete through February 29, 1980, from IMS America. These allow analysis of DAWN-ER reports through the fourth quarter of 1979 and DAWN-ME reports through the third quarter of 1979.

3. Data from various cities on trends in the abuse of propoxyphene. As noted previously, time trend analyses require consistently-reporting ME and ER panels. DAWN provides such panels for all the cities cited during the Health Research Group testimony. The quarterly and annual totals for propoxyphene ER mentions are shown in Table 2, attached, and the propoxyphene ME mentions for the same sites are in Table 3, also attached.

A few key observations about the data in these tables:

- The cities in which it was conceded that propoxyphene misuse has substantially decreased can also be seen to represent the greater number of ME and ER mentions (e.g., Los Angeles, New York, Chicago, and San Francisco).

- Of the cities declared not to exhibit a decrease in propoxyphene misuse, a number do in fact exhibit decreases (e.g., Washington, D.C., Miami, Oklahoma City, Buffalo, San Diego, and Seattle).

- The few cities with stable or increasing numbers of propoxyphene mentions are characteristically already at very low levels (e.g., Indianapolis with 4 ME mentions in 1979, Kansas City with 4 mentions, Minneapolis with 3 mentions, and Norfolk with 5 mentions). Of course, even one propoxyphene ME mention is important -- but it is still accurate to observe that such numbers are too small for meaningful trend analysis.

Table 2

EMERGENCY ROOM VISITORS BY SMSA BY QUARTER
From January 1976 through December 1979

	1976 Q1	Q2	Q3	Q4	Total 1976	1977 Q1	Q2	Q3	Q4	Total 1977	1978 Q1	Q2	Q3	Q4	Total 1978	1979 Q1	Q2	Q3	Q4	Total 1979	Net Change in ER Mentions
Miami	69	72	67	54	256	38	34	31	53	156	47	36	36	16	115	33	23	12	21	89	-167 (-65.2%)
Los Angeles	62	62	62	73	301	69	73	64	38	244	68	52	57	41	212	43	36	46	39	154	-147 (-48.8%)
Philadelphia	87	93	98	100	378	86	85	85	84	340	74	67	79	70	290	78	67	92	58	244	-134 (-35.4%)
Washington, DC	51	43	30	34	198	48	24	28	27	119	27	14	13	23	81	25	17	20	38	82	-116 (-58.6%)
New York	45	49	42	45	181	33	44	48	46	191	29	37	37	26	129	31	18	24	26	99	-82 (-45.3%)
Detroit	63	73	74	89	319	86	68	51	40	286	67	63	63	63	256	77	54	51	54	236	-81 (-25.4%)
Chicago	48	41	53	44	206	43	52	52	59	209	47	47	43	37	174	37	27	30	38	141	-67 (-32.2%)
Other cities	127	126	150	140	543	193	171	193	141	598	144	139	142	133	558	146	106	110	102	482	-63 (-11.6%)
Cleveland	29	39	51	43	162	32	33	27	42	134	29	20	31	30	110	33	23	24	12	92	-50 (-35.2%)
Seattle	13	25	36	29	103	27	19	20	20	86	19	13	21	27	76	17	15	13	13	58	-47 (-44.8%)
San Antonio	33	16	24	24	66	24	25	22	17	88	19	14	13	19	61	13	7	6	16	42	-46 (-51.2%)
Denver	35	38	32	48	153	45	38	36	52	171	41	44	45	36	161	46	36	38	31	125	-36 (-19.6%)
San Diego	30	18	27	30	95	23	18	24	17	84	12	16	15	21	64	21	14	14	19	68	-27 (-20.4%)
New Orleans	10	16	18	9	49	6	12	5	3	26	7	16	23	10	56	11	6	7	6	28	-21 (-42.9%)
Atlanta	29	19	17	25	90	23	26	26	27	101	24	21	29	30	104	23	20	15	14	71	-19 (-21.1%)
Oklahoma City	11	11	9	11	42	11	17	9	15	52	17	10	7	7	41	6	8	7	9	28	-14 (-30.1%)
Dallas	19	19	19	27	84	12	26	17	19	74	24	24	16	21	85	28	17	21	10	68	-16 (-19.0%)
San Francisco	11	9	8	7	31	9	5	13	18	45	13	6	8	11	38	6	5	7	2	22	-9 (-29.0%)
Kansas City	19	17	23	18	81	23	16	22	22	83	21	20	24	15	80	24	15	15	21	75	-9 (-11.0%)
Buffalo	32	25	26	25	108	17	30	43	22	112	33	23	39	27	122	29	20	21	18	98	-8 (-7.5%)
Phoenix	27	33	33	35	128	31	25	32	41	129	37	40	32	28	137	30	28	29	33	120	-8 (-6.3%)
Minneapolis	17	16	21	17	71	23	20	19	17	79	19	15	26	23	83	20	16	16	16	68	-3 (-4.0%)
Indianapolis	29	16	25	32	100	29	34	24	19	106	16	22	15	23	76	25	31	21	22	99	-1 (-1.0%)
Boston	19	23	28	23	103	28	31	37	50	146	43	27	40	34	144	33	42	28	28	130	-33 (+31.4%)
Total					3,837					3,641					3,261					2,723	-1,114 (-20.4%)

Table 3

MEDICAL EXAMINERS MENTIONS BY SMSA BY QUARTER
From January 1976 through September 1979*

	1976					1977					1978					1979					
	Q1	Q2	Q3	Q4	Total 1976	Q1	Q2	Q3	Q4	Total 1977	Q1	Q2	Q3	Q4	Total 1978	Q1	Q2	Q3	Total Q4/78-Q3/79	Net Change in ME Mentions**	
Los Angeles	26	25	15	28	94	29	28	39	17	113	21	19	21	9	70	9	11	9	38	-56	(-59.6%)
New York*	26	28	26	25	103	30	30	17	17	94	17	4	16	16	53	17	18	5	56	-47	(-45.6%)
San Diego	8	7	6	7	28	9	5	6	4	24	6	1	4	3	15	6	3	4	13	-13	(-46.4%)
Washington, DC	1	3	3	5	12	5	2	2	2	11	2	3	0	0	5	1	2	1	4	-9	(-66.7%)
Atlanta	2	4	1	3	10	2	1	1	1	5	0	0	0	0	0	0	3	0	3	-7	(-70%)
Buffalo	6	4	4	2	16	0	2	4	1	7	2	1	3	2	8	4	2	1	9	-7	(-43.8%)
San Antonio	3	3	3	4	12	4	2	1	0	9	0	4	0	4	8	0	3	0	7	-5	(-41.7%)
Columbus City	1	1	1	1	4	2	2	0	0	4	0	3	1	0	4	0	0	0	0	-4	(-100%)
San Francisco	6	9	9	16	40	17	10	13	29	59	10	12	5	13	40	10	5	9	37	-3	(-10.0%)
Cleveland	4	6	3	7	20	2	7	3	6	18	3	3	3	4	13	2	6	5	13	-5	(-13%)
Chicago	12	9	9	12	42	7	13	12	9	41	8	14	18	16	56	8	6	10	40	-2	(-4.8%)
Seattle	1	1	2	0	4	0	1	0	0	1	1	0	2	1	4	0	0	1	2	-2	(-50%)
Denver	5	5	2	0	10	4	5	5	2	16	2	3	1	4	10	3	1	1	9	-1	(-10%)
Atlanta	7	1	2	1	11	10	2	5	3	20	2	4	6	3	15	2	3	3	11	0	0
New Orleans	1	1	0	0	2	0	1	2	1	4	0	2	2	0	4	0	2	0	2	0	0
Philadelphia	6	7	5	2	18	14	9	8	9	40	7	8	4	4	23	8	2	5	19	+1	(+5.4%)
Indianapolis	1	1	0	2	4	0	3	0	1	4	1	1	3	1	6	2	1	2	5	+1	(+25%)
Minneapolis	2	2	0	0	4	3	3	1	0	7	0	0	1	2	3	1	0	2	5	+1	(+25%)
Kansas City	0	0	1	0	1	0	0	3	0	3	4	1	0	0	5	2	1	1	4	+3	(+300%)
Boston	3	1	3	4	11	0	3	6	3	22	13	3	3	2	21	7	6	2	15	+6	(+36.4%)
Buffalo	0	0	2	0	2	1	0	0	0	1	0	1	1	1	3	0	2	3	6	+4	(+200%)
Dallas	2	2	4	2	10	4	3	3	5	15	3	2	4	2	11	6	6	0	14	+4	(+40%)
Miami	1	3	1	3	8	1	2	2	4	9	5	9	7	3	24	4	3	3	13	+5	(+62.5%)
Total					466					327					409				331	-139	(-29.8%)

*Third Quarter 1979 is the most recent ME data which is considered reasonably reliable.

**Net change in mentions from January through December 1976 to October 1978 through September 1979.

In sum, both the national DAWN measures (MEs and ERs) and the city-by-city DAWN data support the conclusion of rapidly declining propoxyphene misuse.

Dr. Bryan Finkle (Director, University of Utah Center for Human Toxicology) has continued to update his independent data base of medical examiner propoxyphene reports. In Table 4, attached, Dr. Finkle's findings are presented organized by the site groups proposed in testimony during the May 21 hearing. As can be seen, the aggregrate decline in propoxyphene ME mentions (1977 to 1979) in those sites in which it was stated that propoxyphene abuse had not declined was, in fact, 50%. By contrast, the aggregrate decline in ME mentions was 56 percent in those sites in which it was agreed that propoxyphene abuse has declined. These two site groups are not, of course, separate. Dr. Finkle's data confirms DAWN reports: propoxyphene misuse/abuse is widely and sharply declining.

4. Codeine abuse increases when propoxyphene use declines. The number of mentions from consistently reporting DAWN-ERs for both propoxyphene and codeine is presented in Chart 2, attached, covering the period 1976-1979. Over these four years, both the decrease in propoxyphene ER mentions and the concomitant increase in codeine ER mentions is obvious. Codeine ER mentions seem to have leveled during the interval 1978-1979.

5. Quantity of propoxyphene acquired by users. An FDA study discussed at the hearing projected nationally that 72,000 people get more than 360 [propoxyphene] pills a month and that 426,000 people get more than 180 pills a month. [2] The FDA study was based on an analysis of 2,985 patient profiles by Pharmaceutical Data Services (PDS). To better understand patterns of propoxyphene use, Lilly also acquired and analyzed a random sample of 3,026 patient profiles from the same source. [3]

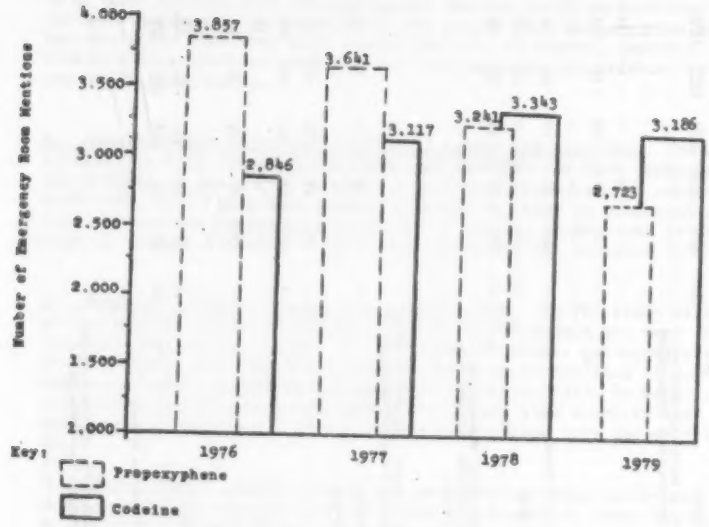
After careful examination of the propoxyphene usage patterns, comparing alternative methodologies and the exception cases identified, it was evident that the original FDA protocol tends to overstate the proportion of the study population acquiring potentially excessive quantities of propoxyphene.

Table 6

MEDICAL EXAMINER CASE REPORTS INVOLVING PROPOXYPHENE
COLLECTED BY DR. BRYAN FINKLE (DIR. UTAH CTR. FOR HUMAN TOX.)

Sites	1971	1972	1973	1974	1975	1976	1977	1978	1979
Sites suggested in Wolfe testimony not to have exhibited decreased propoxyphene abuse:									
Buffalo	-	-	-	-	-	17	13	7	10
Miami	-	2	13	10	19	6	14	11	3
Phoenix	-	-	-	-	-	17	20	15	6
San Diego City & County	-	20	24	23	29	28	30	21	14
Washington, D.C.	-	-	-	-	-	6	3	2	7
SUBTOTAL	-	22	37	33	44	74	80	56	40
Boston, Kansas City, Minneapolis, New Orleans, Norfolk, Oklahoma City, Seattle -- no data								-30%	
Sites conceded in Wolfe testimony to have exhibited decreased propoxyphene abuse:									
Georgia (state)	2	5	6	6	7	10	13	6	11
Illinois (state)	-	-	-	-	-	-	46	44	10
Dallas	-	14	10	16	27	12	17	16	14
Los Angeles	-	37	28	63	55	101	121	64	32
New York City	-	-	-	-	-	14	16	3	12
Philadelphia	-	25	22	28	18	26	29	28	17
San Antonio	-	-	-	-	-	11	8	8	4
San Francisco	-	-	-	-	-	19	16	12	12
SUBTOTALS	2	81	71	113	107	193	272	184	120
Cleveland, Denver -- no data								-56%	
Site suggested in Wolfe testimony to have exhibited increased propoxyphene abuse:									
Indianapolis -- no data									

CHART 2
Project DAWN Emergency Room Mentions
for Propoxyphene and Codeine
1976 through 1979



The following procedural changes from the FDA protocol yielded more reasonable and appropriate results:

- Correcting for equivalent 65 mg dosage (the FDA study did not distinguish between half- and full-strength dosage forms),
- Allowing for unused propoxyphene in the patient's hands at the end of the 30 and 60 day follow-up intervals following the initial prescription,
- Incorporating a longer (60 day) follow-up interval to establish consistency of propoxyphene purchase patterns.

Application of these modifications resulted in the following changes in the study findings:

	Patient Counts (based on Lilly sample)	
	FDA Protocol	Revised Protocol
Low user group (0-180 doses*)	2,473 (97.4%)	2,527 (99.5%)
Intermediate user group (181-360 doses*)	57 (2.2%)	9 (0.4%)
High user group (over 360 doses*)	9 (0.4%)	3 (0.1%)

* In any two consecutive 30 day periods.

Compared to the FDA study, our analysis reveals a lower proportion of the patients acquiring potentially excessive quantities of propoxyphene. Further, the new protocol is conservative in the sense that questionable levels of use tend to be classified high rather than low when compared to average doses per day over the term of therapy.

The national projections of numbers of potential propoxyphene misusers by the FDA staff were based on an estimate of 11.6 million patients exposed to propoxyphene during the period from February through November 1978. They estimated that 426,000 recipients may have been consuming more than the recommended dosage. Of that population, 72,000 were classified into the high user group (those receiving over 360 dosage units in 30 days). Based on the revised study methodology, these projections are substantially overstated.

Since the drug recipients in the PDS system receive prescriptions for a minimum co-payment, the normal marketplace restraints, i.e., the cost of the prescription, are minimized. The potential misuse found, therefore, includes both misuse of the drug product and misuse of the drug benefit program. Other inconsistencies in the data, such as commingled medication for members of the same family or errors in patient identification by age and sex will tend to cause the potential misutilization to be overstated.

Comparison of propoxyphene with codeine products shows a higher potential for codeine misuse at the upper end of the usage range when 65 mg of propoxyphene are compared with 30 mg of codeine. Marketing data clearly indicate that codeine products are the principal analgesic alternative to propoxyphene should propoxyphene become less available for any reason. In light of this, the apparently higher probability of codeine being acquired in abusable quantities argues against decreased propoxyphene availability.

6. Age distribution of abusers/misusers of propoxyphene. As noted in Chart 3, attached, prepared for use in the 1979 propoxyphene meetings [4], the age distribution for all DAWN drugs is not markedly different from the age distribution for propoxyphene. As confirmed in the cumulative frequency distribution in Table 5, attached, the principal analgesic alternatives to propoxyphene advocated by the Health Research Group (aspirin and acetaminophen) have noticeably younger ER age distributions. The ER age distribution for codeine -- the actual alternative analgesic in markets where propoxyphene availability is restricted -- is approximately equivalent to that of propoxyphene. Clearly, the emergency room is the site of treatment most frequently chosen by younger people for drug-related problems, and propoxyphene simply fits the general pattern.

CHART 3

DAWN Emergency Room Mentions, Frequency Distribution by Age

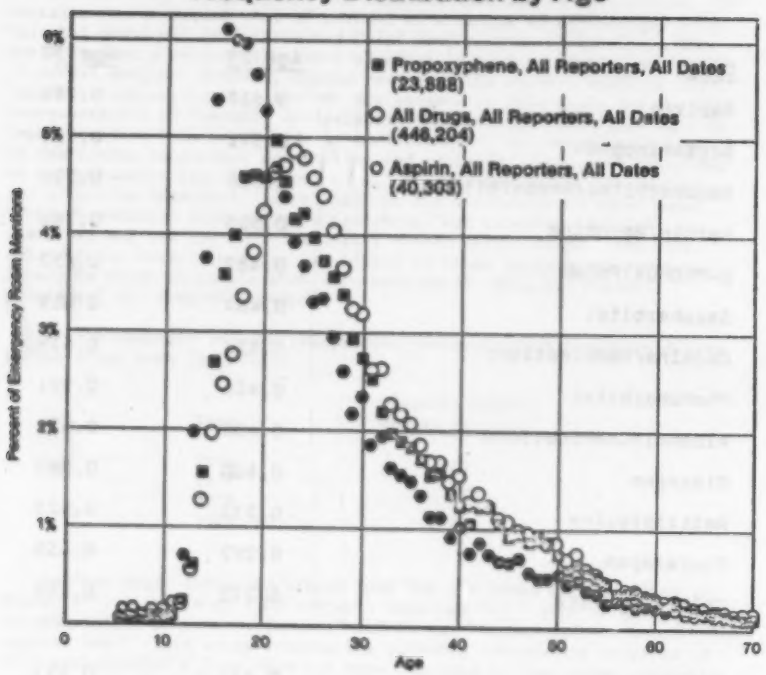


Table 5

PERCENT OF DAWN EMERGENCY ROOM MENTIONS
AT OR BELOW AGE 25 AND AGE 30
ALL MOTIVES, ALL REPORTERS, ALL DATES
(1/1/74 THROUGH 3/31/79)

Drug	Age 25	Age 30
Aspirin	0.617	0.751
Acetaminophen	0.571	0.718
Secobarbital/Amobarbital	0.519	0.716
Heroin/Morphine	0.505	0.766
D-PROPOXYPHENE	0.487	0.652
Secobarbital	0.464	0.619
Codeine/Combinations	0.436	0.619
Phenobarbital	0.426	0.591
Alcohol/Combinations	0.400	0.572
Diazepam	0.400	0.587
Amitriptyline	0.333	0.523
Flurazepam	0.292	0.452
Chloralhydrate	0.272	0.468
All Drugs	0.443	0.627

7. Propoxyphene misuse generally involves persons with antisocial, drug and alcohol problems.

The article, "Propoxyphene and Phencyclidine use in Adolescents" [5] contains the statement that 10 percent of a sample of adolescents with "alcohol problems" in Seattle had "used propoxyphene illicitly". This would suggest a rather high level of abuse if dealing with a population of normal people. However, closer review of the article leads to the immediate conclusion that the 365 adolescents in this study are far from representative of "normal" adolescents. The authors take great care to emphasize that this population of adolescents -- who had been referred by the courts to alcohol counselling and education centers -- exhibited an exceptionally high incidence of alcoholism, antisocial personality and affective disorders. They state in the conclusion of their paper, "These substances [including propoxyphene] are somewhat 'exotic', in that they are not the most frequently abused street drugs. The data consistently reveal that the use of one of these unusual substances is likely to occur in people with more antisocial, drug and alcohol problems." [6] (emphasis added)

Also noteworthy are the independent measures of propoxyphene misuse in the study area (Seattle):

Year	Seattle DAWN-ER Propox Mentions
1976	105
1977	86
1978	76
1979	58

Another study discussed stated that for the seven months ending in March 1977, a sample of 2750 subjects reported "17.7 percent had used [propoxyphene] in their lifetimes" and it was "second only to heroin" in regular use." This study reviews the polydrug consumption patterns of 2750 adolescents, all of whom had been admitted to drug abuse treatment programs [7]. These were not ordinary "teenagers" as one could have concluded without this more careful review of the study. The subjects who had used propoxyphene had also been using an average of six other drugs on a regular basis. Rather than support the proposition that there is a high level of abuse in a normal population, the study confirms the proposition that when propoxyphene misuse occurs, it is predominantly in combination with other drugs or alcohol.

Other comments:

- The period studied includes the peak incidence of both the DAWN-ME and ER mentions of propoxyphene.
- A "lifetime use" percentage of 17.7 is probably not atypical for any 500 subject, post-pubescent sample in the population -- propoxyphene enjoys wide acceptance as an analgesic.
- The DAWN-ER statistics from the study site (Philadelphia) confirm the strong national pattern of declining propoxyphene misuse:

Year	Phila. DAWN-ER Mentions
1976	378
1977	340
1978	290
1979	244

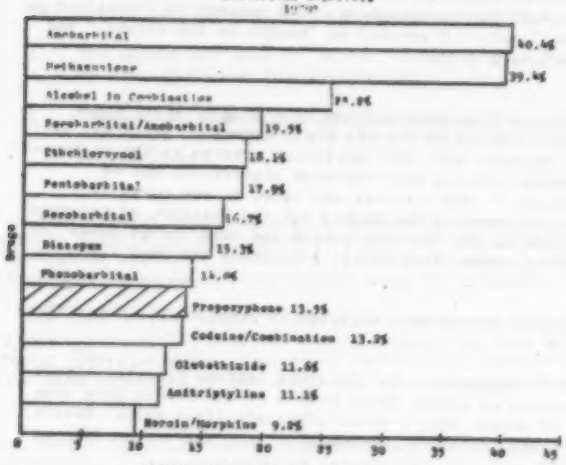
8. The level of propoxyphene use for non-medical psychic effects is not high among "normal" users. It is probable that a sample of overt drug abusers would be disproportionately likely to consume drugs for their "psychic effects." Therefore it is possible in a sample of 926 drug abusers undergoing treatment, that "38 percent would have used propoxyphene for its psychic effects." The source of the propoxyphene was apparently friends, peers, and dealers "70 percent of the time." The broader, national DAWN-ER reports find that only 13.5 percent of propoxyphene ER incidents are motivated by the desire for "psychic effects."

The significance of "psychic effects" in DAWN-ER reports for fourteen separate drugs is illustrated in Chart 4, attached. The significance of "dependence" motives can be seen in Chart 5, immediately following.

Neither psychic effects nor dependence are prominent attributed motives in DAWN-ER propoxyphene reports. To the extent that these are attributed motives for propoxyphene misuse, codeine (the principal analgesic alternative in markets where propoxyphene availability is limited) exhibits equal or greater abuse liability.

CHART 4

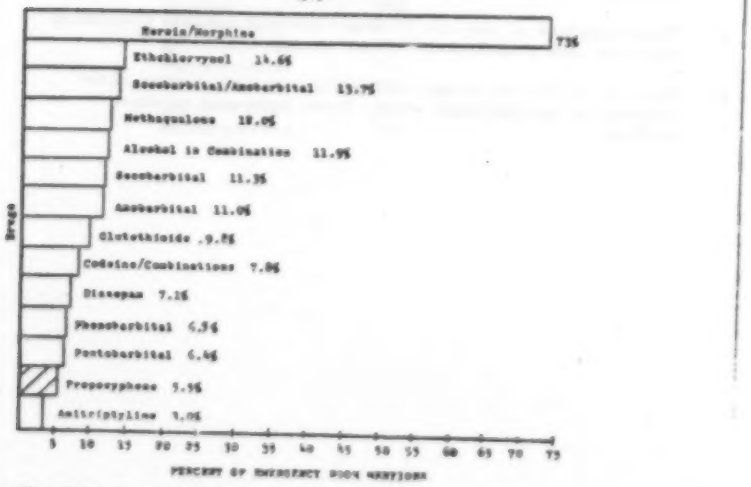
Project DAWN Emergency Room Mentions Where Motivation was Classified as "Toxicic Effects" Consistent Reporters 1979*



*Represents all reports received by IMS America, Ltd. as of 8/29/80.

CHART 5

Project DAWN Emergency Room Mentions Where Motivation was Classified as "Dependence" Consistent Reporters 1979*



*Represents all reports received by IMS America, Ltd. as of 8/29/80.

The 1978 DAWN Annual Report provides data on the source of drugs involved in ER episodes. For propoxyphene, 58.8 percent is classified as "legal prescriptions," only 1.5 percent as "bought on the street," and 1.9 percent "received as a gift."

9. There is no evidence that propoxyphene is a drug of significant abuse. The principal results of the DEA field survey of March 20, 1979, are importantly at variance with the impression created by the statement that "several methadone clinics have reported significant use of propoxyphene by addicts." DEA's survey was based on two types of inquiry: (1) letters to each of the states and the District of Columbia requesting information on the "pattern, scope and duration of abuse" of propoxyphene and (2) a report from each of the DEA's regional field offices.

The results of this survey were analyzed in previous Lilly testimony [8]:

- 18 of the 27 respondents to the state letters reported little or no evidence of abuse, while only 5 of the 27 did note some evidence of abuse. Only 3 state officials (from Maine, Nevada, and New Jersey) endorsed placement of propoxyphene in CSA Schedule-II.
- Only 5.5 percent of the 27 narcotic law-enforcement agencies and police departments responding reported evidence of abuse. Fifty-seven percent report no evidence of abuse.
- Only 11 out of 50 state pharmacy and/or hospital boards that were sampled, reported. Of those 11, only one reported evidence of propoxyphene abuse. Seven of 11 reported no abuse.
- Three-quarters of the the 16 drug-treatment centers responding reported that propoxyphene is not abused.
- Only one of 11 toxicology labs/poison control centers cited evidence of propoxyphene abuse. Three indicated no abuse problem.

Two general conclusions may be drawn from this DEA survey data:

1. The amount and kind of "street abuse" of propoxyphene indicated by the report are sharply limited.

2. There is no significant need or pressure from any substantial number of local authorities for stricter control over propoxyphene.

10. Propoxyphene misuse is only infrequently associated with either "psychic effects" or dependence. Relative to other drugs in DAWN, propoxyphene misuse is infrequently associated with either "psychic effects" or "dependence" [see Charts 4 and 5, attached].

The DAWN "Crisis Center" data are so poorly controlled, so notoriously volatile, that the entire segment has been dropped from the current DAWN system [9]. Therefore, DAWN "Crisis Center" statistics and any claims supported by the statistics are essentially worthless.

11. Statistics on polydrug combinations do not provide meaningful information. Lilly conducted an independent analysis of DAWN polydrug reports during the period 1976-1979. The results for the nine significant, and representative, drugs studied were as follows:

Drug	Number of Unique Combinations Reported
Alcohol	969
Diazepam	668
Codeine	540
Propoxyphene	539
Amitriptyline	501
Phenobarbital	394
Secobarbital	292
Ethchlorvynol	254
Methalqualone	136

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As can be seen, large numbers of "unique combinations" are routine for DAWN reports. Furthermore, the number of combinations offers no clear insight into the abuse liability of various substances; for example, substances which present large and growing abuse problems (like methalqualone) may appear in relatively fewer combinations.

The data presented in the testimony reconfirm that, when propoxyphene misuse occurs, it is predominantly in combination with other drugs or alcohol.

12. Internationally, the pattern of propoxyphene misuse and the extent of abuse is not significantly different than in the United States. A review of the article "Distalgesic Poisoning - Cause for Concern" which was discussed at the hearing reveals that of the 82 patients studied, there were no opiate-like complications in the group taking less than 20 Distalgesic tablets [10]. Opiate complications occurred in only three of the 29 cases where dextro- propoxyphene was taken alone or with drugs other than CNS depressants. The vast majority (87 percent) of complications were caused by taking more than 20 Distalgesic tablets in combination with one or more CNS depressants. This article stresses that propoxyphene overdoses are largely due to "self-poisoning".

The very limited extent of propoxyphene abuse is evident from the 1979 DEA (U.S.) survey. In fact that is confirmed by several of the country responses quoted at the hearing. For example:

Netherlands:	"dextropropoxyphene is occasionally found on a drug abuser."
Norway:	"dextropropoxyphene has occasionally been found..."
Sweden:	"legally obtained preparations containing dextropropoxyphene have to a limited extent been connected with abuse and suicide." (emphasis added)

Other comments about the extent of propoxyphene abuse discussed at the hearing, from Denmark, Philippines, and Portugal, are critical of propoxyphene, but are presented completely without documentation. It was not made clear at the hearing whether any of the other 150(+) member states of the United Nations were sufficiently concerned to respond to the survey -- or if any responded that they were not encountering problems with propoxyphene.

Reference was made to a study by "INTERPOL on appearance of certain psychoactive substances in illicit traffic". Eight countries were cited in which "seizures by police of propoxyphene had occurred in 1977 and 1978." For five of these (Argentina, Canada, Sweden, the U.K., and the U.S.) not even a qualitative description of the extent of the seizures was provided. Specifically, there is no indication that the amount of propoxyphene was significant. For the remaining three countries, the evidence was at best qualitative:

Country	Extent of "Documentation"
Belgium	"...a significant incidence of abuse has been noted..."
Denmark	"also reported a young female addict died from an overdose" [sic]
Hong Kong	"up 'sharply' from 1977 to 1978"

Data on Canadian medical examiner cases involving propoxyphene (complete through year-end, 1979) has been collected by Dr. Bryan Finkle in the province of Ontario. Nearly one-third of Canada's population resides in this single province. His findings were:

Year	Med. Exam. Cases Involving Propox.
1972	44
1973	39
1974	46
1975	42
1976	77
1977	113
1978	111
1979	83

Dr. Finkle's findings confirm the patterns observed in the U.S. sites he also studied: propoxyphene involvement in medical examiner cases peaking in 1977, and declining significantly since then.

Comparison of propoxyphene to codeine incidence of death is not appropriate. Implicit in a statement that propoxyphene is associated with more deaths per million prescriptions than codeine is the assumption that codeine is an adequate and less dangerous analgesic replacement for propoxyphene. Extensive physician testimony, for example in the 1979 propoxyphene investig ions, questions this assumption. While codeine is widely accepted as an analgesic, its side-effects (e.g. constipa ion, dsyphoria, allergic reactions) and its dependence liability are perceived to exceed those of propoxyphene.

Propoxyphene DAWN-ME mentions per thousand new prescriptions rank <u>eleventh</u> among the drugs summerized for the most recent twelve month period. There are also indications in the DAWN-ER data that codeine misuse develops from a somewhat different blend of motives than propoxyphene misuse: dependence figures more prominately, and suicide slightly less prominently, in codeine ER episodes.

Table 4

Project DAWN Medical Examiners' Mentions
Per 1,000 new Prescriptions: in Descending Order;
Contrasted with Absolute Numbers of Medical Examiner Mentions

October 1978 through September 1979*

Medical Examiners Mentions[1]				Number of Medical Examiner's Mentions/1,000	
NO.	Rank	Drugs	New Rx's[2] (000)	New Rx's	Rank
371	1	Heroin/Morphine	373[3]	1.931	1
98	11	Amobarbital	180	.544	2
221	8	Secobarbital/Amobarbital	683	.324	3
160	10	Ethchlorvynol	618	.259	4[t]
226	7	Secobarbital	873	.259	4[t]
186	9	Pentobarbital	932	.195	6
85	12	Methaqualone	726	.117	7
599	2	Amitriptyline	3,697	.108	8
36	13	Glutethimide	382	.094	9
229	6	Phenobarbital	3,034	.075	10
359	3	Propoxyphene	19,021	.024	11
346	4	Diazepam	19,607	.018	12
238	5	Codeine/Combination	34,637	.007	13

*The four most recent quarters for which DAWN ME data are reliable.
1 Basic DAWN mentions reported to IMS America, Ltd. as of 2/29/80.
2 New Prescription Audit, IMS

[3]Based on the estimate for 1978, that there were 373,000 heroin users in the United States. (Heroin Prevalence Estimate, 1978, by Joseph Greenwood, Ph.D., Forecasting Branch, Div. of Resource Development. National Institute on Drug Abuse)

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Table 7

DAWN ME AND ER STATISTICS
Jasinski Methodology*
1976-1979**

Year	DAWN ME			DAWN ER			DAWN (ME AND ER)		
	Propox.	Codeine	Propox/Cod. Ratio	Propox.	Codeine	Propox/Cod. Ratio	Propox	Codeine	Propox/Cod. Ratio
1976	496	203	2.4	3,857	2,846	1.4	4,353	3,049	1.4
1977	563	275	2.0	3,641	3,117	1.2	4,204	3,392	1.2
1978	434	298	1.5	3,241	3,343	1.0	3,675	3,641	1.0
1979	319	233	1.4	2,723	3,186	0.9	3,042	3,419	0.9

*Donald R. Jasinski, "Human Pharmacology of Narcotic Antagonists," Br. J. Clin. Pharm. (1979) 7:287-290.

**All reports from consistently reporting MEs and ERs received by DAWN through 2/29/80.

A review raised by Dr. Jasinski in the hearings utilized DAWN data from the period 1973-1975 in developing support for the claim that the realtive abuse incidence for propoxyphene was higher than codeine for DAWN mentions (2.2 times higher). Although there are a number of limitations to using absolute numbers of DAWN mentions without considering the size of the population exposed to a given substance, Table 7 (attached) presents the results of applying Dr. Jasinski's methodology to the newest DAWN data.

This independent (albeit oversimplified) methodology would suggest propoxyphene's "abuse incidence" is no more, and perhaps less, than that of codeine.

FOOTNOTES

1. Robt. H. Furman, M.D., Statement of Eli Lilly and Company Regarding Propoxyphene, Subcommittee on Health and the Environment, U.S. House of Representatives, May 21, 1980, pages 12-13.

2. D. L. Kennedy, L. B. Burke, "Propoxyphene: An Example of the Need for Increased Pharmacist-Patient Interaction," Amer Pharm, 10: 45-46, 1979.

3. "Patterns of Propoxyphene Use: Analysis of Prescription Records from Pharmaceutical Data Services, Feb-1978 Through Nov-1978," Report from Lilly to FDA (Dr. Judith Jones), April 24, 1980, Exhibit III.

4. T. F. Olsen, "Analysis of DAWN Emergency Room Data," Report from Lilly to DEA (Mr. Howard McClain), March 7, 1979, Figures 1-3.

5. M. A. Schuckit, M.D., E. R. Morrissey, "Propoxyphene and Phencyclidine (PCP) Use in Adolescents," J Clin Psychiatry, 39: 7-13, January, 1978.

6. Schuckit, Ibid., p. 7.

7. E. C. Farley, Y. Santo, "The Abuse of Darvon in a National Sample of Adolescence [sic] Admitted to Drug Abuse Treatment Programs," Phila. Psychiatric Center, Unpublished, Undated.

8. Robt. H. Furman, M.D., Submission of Eli Lilly and Company Regarding Propoxyphene, FDA Drug Abuse Advisory Committee, April 17, 1979, in "Propoxyphene: Public Hearings, 1979," Eli Lilly and Company, Indianapolis, 1979, pages 342-347.

9. Project DAWN Annual Report -- 1978, Drug Enforcement Administation (U.S. Dept. Justice) and National Institute of Drug Abuse (U.S. Dept. Health, Education and Welfare), page 2.

10. R. J. Young, A. A. H. Lawson, "Distalgesic Poisoning -- Cause for Concern," Brit Med J, 280: 1045-1047, 1980.

11. D. R. Jasinski, "Human Pharmacology of Narcotic Antagonists," Brit J Clin Pharmacology, 7:287S-290S, 1979, Table 2 (p. 289S).

Mr. WAXMAN. Thank you very much.

That concludes our meeting.

[The following statement and letters were received for the record:]

STATEMENT REGARDING DEXTROPOXYPHENE

submitted to the

SUBCOMMITTEE ON HEALTH AND ENVIRONMENT
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE
UNITED STATE HOUSE OF REPRESENTATIVES

by

RICHARD DORSEY, M.D., M.B.A.
CHIEF OF PSYCHIATRY
OTTO C. EPP MEMORIAL HOSPITAL
CINCINNATI, OHIO

May 21, 1980

CHAIRMAN: As a practicing physician specializing in psychiatry psychopharmacology, I appreciate the opportunity to submit this ement for the record. One of my special interests is the treatment atients with drug and alcohol abuse, and I have previously testified ood and Drug Administration hearings on dextropropoxyphene (DPX).

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adequate and well controlled studies have shown DPX to be superior lacebo in relieving mild-to-moderate pain. Its efficacy for this led indication has been established beyond reasonable doubt.

tantial clinical experience suggests that DPX is superior to alterna- medications, including aspirin and acetominophen, in relieving nic pain in patients taking the drug over extended periods of time. ring studies are not adequate to confirm or refute this observation, gh testimony by distinguished medical experts at FDA hearings lends redibility.

TY

addiction potential of DPX, particularly in relation to the extent sage, is relatively low, though real. Unlike Schedule II medications, as morphine, meperidine or secobarbital, addiction to DPX occurs emely rarely in patients taking the medication as labeled.

dose deaths do occur with DPX, though these are by definition outside ted usage. The Hamilton County (Cincinnati), Ohio coroner's office identified 4-5 DPX deaths per year for the last few years, nearly all hich have been ruled suicidal. There has been no recent increase in incidence of these deaths. In adjacent Clermont County, a predomi- ly rural area, no DPX deaths have been determined by the Coroner in last 5 years. In neither county has death been reported in patients n to be taking DPX as labeled, alone or in combination with pres- ed doses of other psychotropic drugs, such as tranquilizers or anti- essants.

LATORY QUESTIONS

PX safe and effective when used as labeled? The answer to this question is clearly "yes", icularly with possible modification of labeling to emphasize the risk ethality with overdosage. In this regard, both the benefits and risks of DPX are comparable to those of other medications intended use by the same patient population.

Are Schedule II criteria met? Although DPX has addictive potential, the risk of this occurence is minimal, especially when the medication is taken in accordance with labeling. DPX addiction through street use is quite uncommon in the Cincinnati area. Suicidal overdoses, while regretable, are of limited relevance to scheduling and are relatively few in proportion to the widespread use and availability of DPX. Many drugs of higher overdose lethality than DPX (e.g., anti-coagulants, insulin, digitalis preparations, tricyclic anti-depressants) are not scheduled at all, nor should they be.

Would placing DPX in Schedule II serve the public interest? Overall, the answer to this question has to be "no". Schedule II would reduce the availability of DPX to the large majority of appropriate users by eliminating telephone prescriptions and refills. Both would result in an unnecessary increase in visits to physicians, and would eliminate the doctor's option to prescribe small numbers of capsules with periodic refills as a means of controlling inappropriate use. The burden of these changes would fall disproportionately on public-sector patients, for whom clinic visits are especially draining of time, energy and money. Also, a shift to other similar medications would occur with no net gain in safety or efficacy.

In addition, the addictive substances which constitute the greatest public health hazards, alcohol and tobacco, remain freely available to every individual. Proposing Schedule II for DPX, already available on prescription only, while largely ignoring hundreds of thousands of annual deaths from non-prescription recreational substances, surely constitutes a classical example of straining at a gnat and swallowing a mule.

CONCLUSIONS

The more stringent drug regulation sought by healthy, affluent "consumerists" frequently produces perverse effects for typical patients. Decreased medication availability and increased cost commonly occur, and would be the likely result of re-scheduling DPX. DPX is safe and effective when used as labeled and subject to Schedule IV controls. The Food and Drug Administration has correctly concluded that no additional regulatory action is needed, with the exception of increased emphasis in labeling on the risks of overdosage and abuse.

The best interests of the patients of Cincinnati would be served by leaving DPX in Schedule IV, and more broadly by reducing rather than increasing regulatory burdens on the pharmaceutical industry. The "drug lag" may not bother "consumerists", but it certainly concerns the patient who does not respond satisfactorily to existing medications, and the physician who spends his professional life treating such patients.

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June 6, 1980

The Honorable Henry A. Waxman
Chairman, Subcommittee on Health and
the Environment
Committee on Interstate and Foreign Commerce
U. S. House of Representatives
2415 Rayburn House Office Building
Washington, DC 20515

Re: Darvon Hearing

Dear Congressman Waxman:

During the recent propoxyphene hearing, questions were raised with respect to whether or not physicians had adequate knowledge of the proper use of Darvon. IMS America Ltd. has participated in the development of information to assist in appraisals of physicians' knowledge on this subject. I am pleased to offer the following comments for the record of these proceedings relevant to that subject.

During the hearings FDA representatives noted that the IMS National Detailing Audit was utilized by the Food and Drug Administration to measure physicians' perceptions regarding appropriate prescribing information for Darvon. Although we feel the IMS National Detailing Audit is an excellent source of market information for certain purposes, it was not designed for and is not particularly suitable for the purpose of determining the scope of warning information provided physicians under a program such as the one Eli Lilly and Company conducted. The Audit will only afford a highly summarized version of the detailed message and is therefore not an adequate measure of the Lilly program.

A more appropriate study of physicians' knowledge was conducted by IMS America Ltd. in April of 1980. In that study IMS interviewed by telephone 460 physicians randomly selected from three physician lists - The IMS National Detailing Audit panel, a Lilly list of frequently detailed physicians, and a Lilly list of infrequently detailed physicians. The subject of the interview was physician awareness of precautions when prescribing Darvon.

The data show that 88 percent of physicians interviewed report awareness of precautions associated with prescribing Darvon. Although physicians are probably biased toward giving a conservative answer--i.e., precautions of some sort should be observed with prescribing any drug--an 88 percent affirmative response rate is considered exceptionally high and a valid indicator of special awareness of precautions associated with Darvon.

Physicians then were asked to volunteer which precautions they consider when prescribing Darvon. Physicians were not read a list of possible problem areas, but rather asked to search their own memories for information on Darvon precautions. This "unaided" recall is considered a more rigorous measure of true awareness than "aided" recall, where precautions are listed by the interviewer to assist physicians with their answers. A very large majority of physicians specified dangers of additions, abuse, or harmful interaction with alcohol or other CNS depressants. While not all physicians named each of these precautions, in unaided response questions during telephone interviews physicians typically give answers which fail to reveal the breadth of their knowledge on the subject under consideration. Responses given in this situation represent the "tip of the iceberg" of doctors' actual information. The correct interpretation of the data in this IMS study is that the vast majority of physicians in the survey are aware of abuse problems associated with Darvon prescribing.

Very truly yours,

Franklin T. Osgood, Jr.

Franklin T. Osgood, Jr. mcm
President

FTO/mcm

STATE OF RHODE ISLAND AND PROVIDENCE PLANTATIONS

Department of Health
OFFICE OF STATE MEDICAL EXAMINERS
48 Orms Street
Providence, R. I. 02904

June 18, 1980

Henry A. Waxman
Chairman, Subcommittee on
Health and the Environment
512 House Annex #1
Washington, DC 20515

Dear Representative Waxman:

Pursuant to your request to submit written testimony with reference to the abuse of the drug propoxyphene, I would like strongly to support the efforts made by the concerned community of scientists and lay people to implement a more stringent control of this very dangerous substance.

The facts continue to show that fatalities, after an initial decrease, are leveling off and may well resume climbing in the next several years, that along with continuing abuse fatalities, many "accidental" deaths may be taking place due to cardiac arrhythmia produced by the metabolite norpropoxyphene, that Eli Lilly Company has peddled the drug as an alternative analgesic, when in fact it is really a sedative not unlike methadone, and finally, the fact as to whether propoxyphene is therapeutic in any sense when compared to other analgesics such as codeine, asprin, etc., is unclear.

Our experience in the State of Rhode Island over the past six years indicates that the number of fatalities from propoxyphene, albeit decreasing during 1979, now are again increasing with the total number of cases for the first half of 1980 already equalling that for the entire previous year of 1979! Quite obviously, the warnings put out by the company(s) and other reminders in the press, both locally and nationally, have done little to stem the tide of use and abuse of propoxyphene. We have found it necessary, for example, just recently to bring to the attention of our Board of Medical Review the improper prescription practice of a physician to a Darvon(R) addict of seven years, (supposedly unknown to him) in which 500 capsules had been prescribed over a seven month period with the patient ultimately dying of acute and chronic propoxyphene and norpropoxyphene intoxication. Similar examples are continuing to occur, and there seems to be no end in sight to Darvon(R) deaths in this State.

Since the World Health Organization has recently recommended that propoxyphene be place in Schedule II, and since many of the features of this drug, especially the potential for abuse, suggests that indiscriminate prescription practices can dramatically increase the number of addicted patients, I would strongly favor the Committee recommending a reschedule of all forms of propoxyphene into Schedule II at the earliest possible moment. This would not only save lives, and

lessen addiction, but would offer more rational choices for prescribing physicians, while also decreasing the needless prescribing practices in many clinics and emergency rooms which take place under less than optimal circumstances for minor symptomatology for myriads of unaware and uninformed patients.

Parenthetically, the response of many worried scientists that have been expressed to JAMA following their article and editorial of April 20, 1979, have laid dormant because of their refusal to publish same. I enclose a copy of my concerns for your information and hopefully it can be appended to the record.

Very truly yours,

William Q. Sturner, M.D.
Chief Medical Examiner
State of Rhode Island

WQS/pc
Enclosure

STATE OF RHODE ISLAND AND PROVIDENCE PLANTATIONS

Department of Health
OFFICE OF STATE MEDICAL EXAMINERS
48 Orms Street
Providence, R. I. 02904

May 5, 1979

Editor, JAMA
535 N. Dearborn Street
Chicago, Illinois 60610

THE FABLE OF PROPOXYPHENE

When Simple Johnnie was made King and given a wife, a crown and a throne, Hans Christian Andersen tells us that such information "we have still fresh from the newspaper of the editor and the reporters--and they are not to be believed for a moment."

Your coronation of propoxyphene in the April 20, 1979 issue was produced by specious arguments for its acceptability such as . . . Yes, Virginia . . . suicidal window jumping! You would, of course, support doctors writing prescriptions for houses without windows for "medical reasons"! But how ludicrous to suggest, indeed lend support, to the proposal that propoxyphene be dispensed over the counter. A Lilliputian mentality at work! How about methadon at your local Drive-In? Self-diagnosed pain should only hurt for a little while. And anyway, "the doctor can't see you until next month . . ."

Since "downwind" testing of atomic weapons and the indiscriminate use of pesticides have also been employed for some twenty years in "billions of doses", it is likely that our population has been "completely duped" in several arenas (by our "protectors", no less) and for you to sanction the meritorious value of anything because of sheer numbers and longevity is straining believability, if not downright scandalous!

More to the point, it has been shown in the literature, fatality statistics, and yes, publicly recounted in your maligned Senate hearings, that propoxyphene is toxic, addicting, and unsafe alone, with perilous results when combined with alcohol and other drugs. Furthermore, not only have the Mayo Clinic and other studies shown its lack of effectiveness as an analgesic (somewhere between sugar pills and two aspirins) but its "pain-killing" effect has never been shown to be more or less than its obvious sedative activity--the wholesale pharmaceutical misrepresentation that is the bottom-line of the "clinical effectiveness" argument.

Now, it turns out, that the metabolite, norpropoxyphene, whose half-life and thus build-up in the body exceeds that of the parent drug, may be responsible for cardiac arrhythmia, a factor leading more scientists and physicians to question the long-term use of this substance, not to mention those who now refrain from prescribing it altogether. How many extra seconds does it take to write a Schedule II prescription? Could it prevent a potential addict or even save a life? What will (should) the prudent physician do?

All of which leads me to believe that if we are about to embark on a "fairy tale" explanation for the practice and policy of medicine, I am drawn to the likely response of St. George when he shockingly discovers that the maiden had all along been having an affair with the dragon!

William Q. Sturner

William Q. Sturner, M.D.
Chief Medical Examiner, State of Rhode Island
Associate Professor of Pathology
and Community Health, Brown University
Director, Subsection of Forensic Medicine

[Whereupon, at 1:33 p.m., the hearing was adjourned.]

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